

The Heterogeneity of Oral Immunotherapy Clinical Trials: Implications and Future Directions

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Abstract Food allergy is a potentially life-threatening disease which affects up to 8 % of children and 2–3 % of adults. Increasing food allergy prevalence poses a major public health concern. Induction of desensitization to food allergens through oral immunotherapy (OIT) is an expanding area of study encompassing peanut, egg, milk, and other food allergens. OIT consists of administering incremental doses of food allergen to food-allergic patients, to induce a state of desensitization. Safety, tolerability, and efficacy all remain ongoing concerns. Clinical trials for oral immunotherapy have encompassed many variations, including differences in dosage sizes and frequency, duration of build-up, type of allergen used, patient characteristics, and adjuvant therapies. Consequently, studies have also shown variation in rates of adverse effects, and successful desensitization. Here, we provide an overview of the key studies and discuss the implications of this heterogeneity. While desensitization is successful in the majority of patients, only a minority appear to develop sustained unresponsiveness even after years of therapy. Much larger and longitudinal studies using more homogenous protocols are needed in order to evaluate the clinical applicability of OIT, its long-term effectiveness, and effect on quality of life. The role of adjunctive therapies, including omalizumab and probiotics, requires further evaluation.

Keywords Food allergy · Oral immunotherapy · Desensitization · Sustained unresponsiveness

Abbreviations

BAT	Basophil activation test
CM	Cow's milk
DB	Double blind
DBPCFC	Double-blind placebo-controlled food challenge
FC	Food challenge
N/A	Not available
OFC	Oral food challenge
OIT	Oral immunotherapy
PC	Placebo controlled
QoL	Quality of life
RCT	Randomized controlled trial
Specific-IgE	s-IgE
SU	Sustained unresponsiveness
Treg	Regulatory T cell

Introduction

Food allergy is a potentially life-threatening condition that affects up to 6–8 % of children and 2–3 % of adults [1–4]. Incidence of food allergies has increased significantly over the past 20 years [5]. While most children with hen's egg (HE) and cow's milk (CM) allergy naturally develop tolerance to these foods over time [6–8], spontaneous resolution of peanut or tree nut allergies has been observed in less than 20 % of patients [9–11]. This poses a major concern, since peanut and

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tree nut allergies account for the majority of fatal or near-fatal food allergic reactions [12, 13].

There is currently no cure for food allergy [14, 15]. Standard of care consists of food avoidance and keeping epinephrine and antihistamines readily available [16, 17]. Patients and their families may experience significant food-related anxiety, fear of accidental exposures, and social and dietary limitations, which negatively affect quality of life (QoL) [18–20].

Oral immunotherapy (OIT) has gained momentum over the past decade and is currently one of the most actively evaluated approaches in food allergies. Most protocols consist of three successive stages: initial dose escalation, up-dosing, and maintenance (Fig. 1). Escalation begins with incremental administration of very small amounts of food allergen, below the threshold of reactivity, usually over 1–2 days. Up-dosing starts with daily ingestion of the highest tolerated dose, with doses increased usually weekly or biweekly until the maintenance dose is reached. In the maintenance phase, patients consume the food regularly (usually daily) for months or years. Desensitization is defined as the ability to tolerate a higher threshold of food allergen without allergic reaction, while consuming the food regularly. Permanent tolerance or cure is defined as the absence of symptoms after ingestion of the food, even after prolonged and/or variable periods of avoidance. Sustained unresponsiveness (SU) is defined by the ability to retain the increase in threshold reactivity after the food ingestion has been stopped for a defined period of time, usually weeks to months. SU is considered achieved if a subject successfully tolerates all doses of a double-blind placebo-controlled food challenge (DBPCFC).

OIT has been evaluated for different foods, including peanut [21–26, 27•], cow's milk [28–31], hen's egg [32–47], and wheat [48–50], as well as for multiple foods concomitantly [51, 52] (Tables 1, 2, 3, and 4). Most studies have focused on peanut, milk, or egg. While desensitization has been successful in the majority of the trials, there has been tremendous variability in the approach at almost all levels: study design (open label versus double blinded, placebo-controlled or randomized controlled trials (RCTs), multi-site versus single-site), type of food allergen (natural versus modified form) and vehicle used, duration and dosing in each OIT phase,

the target maintenance dose, grading and reporting of adverse reactions, the target dose during the exit DBPCFC, inclusion and exclusion criteria for enrollment as some studies excluded patients with severe allergies, or used performance of a dose-limiting oral food challenge (OFC) or reliance on allergy history and/or food-specific skin and specific-IgE (s-IgE). More recently, adjunctive therapies to OIT have been evaluated, including the use of anti-IgE antibody [58, 70, 71••, 77, 78] leukotriene receptor antagonists [79] and probiotics [60].

Compared to desensitization, SU has been evaluated in far fewer trials. There has also been heterogeneity in the approach to evaluating SU, as different studies have varied both the duration of maintenance and the abstinence period (2 weeks to few months), sometimes within the same trial [25, 32, 33, 44, 47, 54••, 60, 71••, 74••, 75].

Here, we will provide an overview of key clinical trials of peanut, milk, and egg OIT to highlight their heterogeneity. We will discuss the potential implications of such variability and future directions of OIT.

Peanut OIT

Case reports of peanut OIT were first described in 2006 [26, 80]. The first open-label clinical trial of peanut OIT was published in 2009 [24, 53]. Thirty-nine pediatric patients received OIT with defatted peanut flour (50 % protein), in a 36-week protocol using 1-day dose escalation from 0.1 to 50 mg peanut protein, then biweekly up-dosing up to 300 mg. Seventy-one percent of 39 patients enrolled successfully reached the 300 mg maintenance daily dose, and 69 % of enrolled patients passed a peanut OFC (a cumulative dose of 3900 mg peanut protein) after 4–22 months on daily maintenance dose. Thirty-six patients (93 %) had some symptoms during initial escalation day, and four of them required epinephrine injection. All subjects experienced rare, and mostly minor, symptoms during the home dosing of the buildup/maintenance phases (3.7 % of 14,773 doses given).

A long-term, open-label study examined the ability of these patients to develop SU after up to 5 years of OIT [54••]. The protocol was modified over time to increase the maintenance to 4000 mg. Of the 39 patients initially enrolled, 24 (61 %)

Fig. 1 Design of oral immunotherapy clinical studies. A representative schematic of clinical OIT trial is shown. Specific protocols may not include all steps, and food challenges were not always performed at each stage

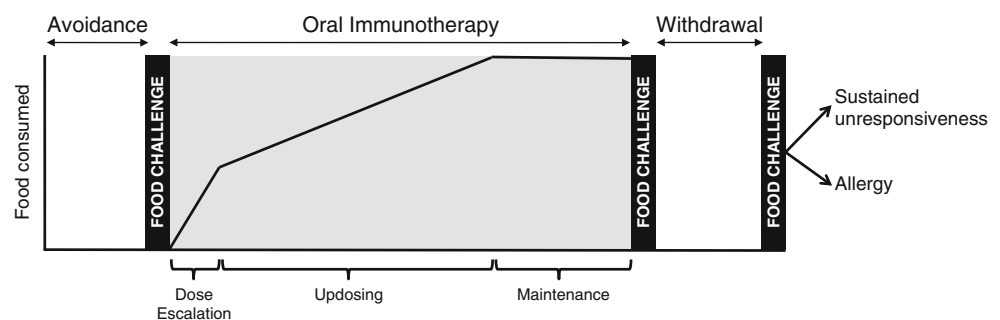


Table 1 Peanut OIT studies

	No. of patients, ages	Food allergen	Study design	Entry criteria	Initial dose escalation	Up-dosing	Maintenance	Desensitization results	Long-term results	Adverse events	Laboratory results	Notable features
Hofmann et al. 2009 [53] Jones et al. 2009 [24]	39, 1–16 years	Peanut flour.	Open label, not controlled.	Clinical history of reaction, +SPT, peanut IgE >7 kU/L. Median peanut IgE 85.4 kU/L.	1 day, 0.1–50 mg (90 mg cumulative), doubling every 30 min.	Biweekly increase by 25 up to 300 mg.	300–1800 mg daily for 4–22 weeks (total 36 weeks OIT).	71 % reached 300 mg daily dose.	69 % (27/39) passed OFC at 1800 mg (total 3.9 g).	Escalation: 92 % symptomatic, 15 % needed epinephrine. 3.7 % of 14,773 doses during up-dosing or maintenance, mostly minor.	↓ peanut IgE and total IgE, ↑ peanut IgG4 at completion. Transient ↑ in Ara h2-responsive Tregs.	Feasibility of peanut OIT
Blumchen et al. 2010 [22]	23, 3–14 years	Crushed roasted peanuts.	Open label, not controlled.	Peanut IgE >0.35 kU/L. Severe asthma excluded. DBPCFC ≤500 mg total. Median peanut IgE 95.6 kU/L.	7 days, 2–4 increases/day, to maximum of 500 mg or double max dose in DBPCFC.	~20 % increase every 2–4 weeks for 0–20 months.	≥500 mg for 8 weeks.	61 % (14/23) reached 500 mg daily for 8 weeks.	After 2 weeks off OIT, 14/23 (100 % who reached maintenance) tolerated 500 mg in DBPCFC, 17 % tolerated 4 g.	Escalation: subjective symptoms with 25/317 (7.9 %) doses. Reactions with 160/6137 (2.6 %) of buildup/maintenance doses.	↓ peanut SPT, ↓ peanut IgE, ↓ peanut IgG4, ↓ IL-4, IL-5, IL-2 from PBMC in completers.	Patients with allergic co-morbidities and risk factors for systemic reactions
Varshney et al. 2011 [27•]	28, 1–16 years	Peanut flour.	RCT, placebo controlled, double blind (2:1 OIT/placebo).	Clinical reaction history, +SPT, peanut IgE >15 kU/L (>7 if recent reaction), severe anaphylaxis excluded. Median peanut IgE 104 kU/L (OIT), 57 kU/L (control).	1 day, 0.1–6 mg Q30-min intervals.	Biweekly, 25–100 % increases for 44 weeks to 4000 mg daily.	Up to 4000 mg daily for 1 month.	80 % on OIT tolerated 4000 mg daily for 1 year, 80 % on OIT passed 5000 mg DBPCFC after 1 year.	N/A	Escalation: 47 % (9/19) of OIT had symptoms, 2 required epinephrine. Reactions with 1.2 % of buildup/maintenance doses.	↓ peanut SPT, ↑ peanut IgE, ↑ peanut IgG4, ↑ Treg ratio, ↓ IL-5, IL-13.	RCT
Vickery et al. 2014 [54••]	39, 1–16 years	Peanut flour.	Open label, not controlled (enrolled patients from [53] and [24]).	Clinical reaction history, +SPT, peanut IgE >15 kU/L (>7 if recent reaction), severe anaphylaxis or severe asthma excluded.	1 day, 0.1–50 mg, doubling dose Q30min to maximum tolerated dose.	Biweekly, by 100 % to 50 mg then by 25-mg intervals to 300 mg daily.	300 mg daily, or if pass OFC at 3900 mg, increase to 1800 mg daily, then 4000 mg daily for 5 years.	66 % (26/39) reached 4000 mg daily.	After 4 weeks off OIT, 31 % (12/39) tolerated 5000 mg OFC and open dose.	15 % withdrew for allergic side effects.	↓ peanut SPT in patients who passed vs. failed OFC/open dose. ↓ peanut IgE, ↑ peanut IgG4, but level not associated with clinical outcome.	Long term, evaluation of SU
Anagnostou et al. 2014 [55••]	99, 7–16 years	Peanut flour	RCT, placebo controlled, double blind. (OIT/placebo), control group crossed over to active OIT.	Clinical reaction history, DBPCFC ≤1400 mg, severe anaphylaxis or severe asthma excluded.	None.	Biweekly from 2–800 mg.	800 mg daily for 26 weeks (phase 1)	Phase 1: 84 % OIT, 0 % placebo passed 1400 mg DBPCFC. Phase 2: placebo patients switched to OIT, 54 % passed same DBPCFC.	Phase 1: 62 % OIT, 0 % placebo tolerated 800 mg daily at 26 weeks. Phase 2: placebo patients switched to OIT, 91 % tolerated 800 mg daily at 26 weeks. QoL improved in both groups.	Up-dosing: Mild adverse events in 6.3 % of doses. 1 patient received epinephrine on 2 separate reactions.	After 24 weeks OIT: ↓ peanut SPT, ↑ peanut IgE. No significant difference in peanut in vitro basophil activation test before/after OIT.	Double Blind, Placebo RCT, large scale comparison.

Table 1 (continued)

	No. of patients, ages	Food allergen	Study design	Entry criteria	Initial dose escalation	Up-dosing	Maintenance	Desensitization results	Long-term results	Adverse events	Laboratory results	Notable features
Narisety et al. 2014 [25]	21, 7–13 years	Aqueous peanut extract.	RCT, parallel intervention, double blind (1:1 OIT/SLIT).	+SPT, DBPCFC ≤1000 mg, severe anaphylaxis or severe asthma excluded, median peanut IgE 1.69 (OIT), 1.63 (SLIT) kU/L.	1 day 0.1–6 mg OIT, 0.000165–0.066 mg SLIT.	Weekly to biweekly up-dose for 16 weeks.	2000 mg OIT, 3.7 mg SLIT daily for 6–12 months.	50 % SLIT, 45 % OIT passed OFC 1 log at 6–12 months.	Sustained unresponsiveness: 50 % (2/4) OIT, 20 % (1/5) SLIT passed repeat OFC 10 g after 4 weeks peanut avoidance.	Reactions to 43 % of OIT, 9 % of SLIT, 5 OIT reactions required epinephrine, 1 OIT patient developed eosinophilic esophagitis and withdrew.	Both OIT and SLIT: ↓ peanut SPT, ↓ peanut IgE after IT.	Comparison of SLIT vs. OIT, evaluation of SU.
Syed et al. 2014 [56]	43, 5–45 years	Peanut flour.	RCT, open label (OIT/peanut avoidance).	SPT ≥10 mm, peanut IgE ≥15 kU/L, DBPCFC ≤100 mg. Severe asthma excluded.	1 day 0.1–6 mg (cumulative 12 mg).	Biweekly up to 4000 mg, 24 months.	4000 mg daily, up to 24 months.	20/23 OIT, 0 % (0/20) control desensitized (passed DBPCFC 4 g) at 24 months.	SU after off peanut OIT for 3 months, 30 % (7/23) passed DBPCFC at 27 months. After off peanut for 6 months, 13 % (3/7 SU, 3/23 ITT) remained tolerant (passed DBPCFC).	N/A	OIT group: ↓ peanut BAT, ↓ peanut SPT. Patients with SU at 30 months had ↑ ai-Treg with greater suppressive function, and with higher levels of FOXP3 hypomethylation.	Longer evaluation of SU, more elaborate evaluation of Tregs.
Bird et al. 2015 [57]	55, 4–21 years	Peanut flour (AR101).	RCT, placebo controlled, double blind (1:1 OIT/placebo).	Clinical reaction history, +peanut IgE or SPT, DBPCFC ≤100 mg.	None.	Biweekly.	300 mg daily.	79 % OIT, 27 % placebo reached maintenance. Of those, 62 % OIT and 0 % placebo tolerated 1043 mg in DBPCFC.	In progress.	72 % OIT, 27 % placebo had GI side effects, 1 patient required epinephrine.	In progress.	RCT standardized pharmaceutical product.
Schneider et al. 2013 [58] Burton, et al. 2014 [59]	13, 7–25 years	Peanut flour, omalizumab.	Open label, omalizumab + OIT.	Clinical reaction history, +SPT, peanut IgE >20 kU/L, total IgE 50–2000 kU/L, DBPCFC ≤100 mg (186 mg cumulative)	1 day 0.1–500 mg (992 mg cumulative). 100 % reached 500 mg dose on the first day.	Weekly, 750–4000 mg, 7–12 weeks.	4000 mg daily for 12 weeks.	Off omalizumab 10–12 weeks, 85 % passed DBPCFC 8000 mg, 92 % passed OFC.	In progress.	Escalation: 46 % had mild (grade 1) reactions. All doses: 2 % of 70 kU/L before/70 kU/L after OIT). Peanut IgE antibodies in post-OIT sera suppressed basophil activation [59].	Peanut IgE ↓ but still elevated (median 229 kU/L before/70 kU/L after OIT). Peanut IgE antibodies in post-OIT sera suppressed basophil activation [59].	Use of omalizumab as adjunct to OIT.
Tang et al. 2015 [60]	62, 1–10 years	Peanut flour, lactobacillus 2 × 10 ¹⁰ CFU daily (probiotic).	RCT, placebo controlled, double blind (Probiotic + OIT vs. placebo + OIT).	Clinical reaction history, +SPT, peanut IgE. Optional OFC: (peanut IgE >8 stratified in randomization).	1 day, 0.1–12 mg (total 24 mg), 8 steps.	Biweekly 25 mg, 2 g, 8 months.	2 g daily for 10 months (18 months OIT total).	90 % probiotic + OIT, 7 % placebo desensitized (DBPCFC).	Sustained unresponsiveness: 82 % probiotic, 4 % placebo (DBPCFC 2–5 weeks after probiotic discontinued).	45 % probiotic, 32 % placebo patients had ≥1 severe adverse event, 1 patient had anaphylaxis to probiotic.	↓ peanut IgE and ↑ IgG4 in probiotic patients, but not in placebo.	Use of lactobacillus/probiotic as adjunct to OIT and possible sustained tolerance

↓ means decreased; ↑ means increased

Table 2 Milk OIT studies

	No. of patients, ages	Food allergen	Study design	Entry criteria	Initial dose escalation	Up-dosing	Maintenance phase	Desensitization results	Long term results	Adverse events	Laboratory results	Notable features
Meglio et al. 2004 [30] Meglio et al. 2008 [61]	21, 5–10 years	Fluid milk	Open label, not controlled.	History of clinical reaction (3) or DBPCFC ≤ 125 mL milk (21).	None	Weekly, <1 drop-200 mL (0.06–6400 mg) until 70 mL then every 16 days until 200 mL, 6–8 months.	Up to 200 mL daily or milk-containing foods, up to 61 months.	71 % (15/21) tolerated 200 mL, 14 % (3/21) reached 40–80 mL. Mean duration 201 days (range 183–234 days).	After 48–51 months, 70 % in follow-up (14/20) tolerating some milk. 43 % (9/14) taking milk ad lib.	Desensitization: 3/21 (14 %) had mild symptoms so discontinued; 3/21 (14 %) had symptoms so took lower daily dose. Follow-up: no reactions requiring epinephrine. Reactions in 3 OIT, 0 control patients.	↓ IgE and SPT positivity for casein and α -lactalbumin in tolerant patients (long-term follow-up).	Pilot protocol, long-term follow-up, home up-dosing.
Morisset et al. 2007 [40]	57, 1–6 years	Fluid milk.	RCT, open label (OIT/milk-free diet).	Clinical history, +milk IgE, positive SBPCFC (but those reacting to ≤ 60 mL milk excluded?).	None.	Unknown.	6 months.	After 6 months, 11 % OIT and 40 % control had positive SBPCFC (<200 mL).	N/A	Reactions in 3 OIT, 0 control patients.	↓ milk SPT wheal in OIT, ↑ in control.	RCT
Longo et al. 2008 [29]	60, 5–17 years	Fluid milk, then foods with milk.	RCT, open label, (OIT/milk-free diet).	Milk IgE >85 kU/L, DBPCFC ≤ 0.8 mL, history of severe reaction.	10 days, up to 20 mL milk in 1–2-h intervals.	Every other day, increase by 1 mL (home setting), to 150 mL daily, 3 months.	150 mL (4800 mg) daily then milk containing foods for 1 year.	At 1 year, 37 % (11/30) OIT fully desensitized to 150 mL daily, 53 % (16/30) OIT partially (5–15), 0 % control passed DBPCFC.	N/A	Desensitization: 4 patients required IM epinephrine. Home dosing: 2 required epinephrine. 20 % control had adverse reaction to accidental milk.	↓ milk IgE after OIT in 50 % (15/30), no difference in control.	RCT, severe milk allergy patients.
Skpirak et al. 2008 [31] Narisetty et al. 2009 [62] Keet et al. 2013 [63••]	20, 6–21 years	Milk powder.	RCT, placebo controlled, double blind, then open-label crossover. (2:1 OIT/placebo)	Clinical history, +SPT or milk IgE >0.35 kU/L, DBPCFC ≥ 2.5 g. Severe anaphylaxis, severe asthma excluded. Median milk IgE 31 kU/L.	1 day 0.4–50 mg, 30-min increments.	Weekly or biweekly to 500 mg for 8 weeks.	500 mg daily for 13 weeks then DBPCFC up to 8 g, if pass, then up-dose at home (median of 7000 mg). If pass, 3rd DBPCFC 16 g then 5 years maintenance.	23 % OIT, 0 % placebo, 67 % crossover OIT passed DBPCFC (8000 mg); 92 % active OIT, 0 % placebo, 83 % of cross-over OIT tolerant to ≥ 2540 mg.	At 5 years: 19 % of 13 in follow-up tolerating unlimited milk, 31 % 1 serving/day, 34 % limited amounts, 16 % no milk/avoiding completely.	Desensitization: reactions to 45 % of 2437 doses in OIT, 11 % of 1193 in placebo patients. 4 patients required epinephrine. Follow-up open label OIT: reactions in 17 % of 2465 home doses.	No significant change in milk IgE in OIT after desensitization. ↓ milk IgE and milk SPT in long-term follow-up.	Double blind RCT, long-term follow-up.

Table 2 (continued)

	No. of patients, ages	Food allergen	Study design	Entry criteria	Initial dose escalation	Up-dosing	Maintenance phase	Desensitization results	Long term results	Adverse events	Laboratory results	Notable features
Caminiti et al. 2009 [64] Pajno et al. 2010 [65]	30, 4–10 years	Fluid milk.	RCT, single blind, placebo controlled (OIT/placebo).	Clinical history, +milk IgE, +SPT, DBPCFC <150 mL. Median milk IgE 33 kU/L OIT, 25 kU/L control.	None.	Weekly in clinic, 1 drop of 1:25 dilution—200 mL undiluted, 18 weeks.	200 mL (6400 mg) daily.	67 % milk OIT desensitized, 0 % placebo (DBPCFC 200 mL).	Reported in Pajno et al. 2013 [66].	Desensitization: 10/13 OIT patients had symptoms, 2 required epinephrine. No placebo patients reacted.	At 18 weeks, no Δ in milk IgE for OIT or control. $\uparrow$ milk IgG4 in OIT, not control.	RCT
Pajno et al. 2013 [66]	32, 4–13 years	Fluid milk	RCT, open label, comparison of maintenance regimens.	Clinical history, +milk IgE, +SPT, DBPCFC <150 mL. Included patients from [65].	None	N/A	150–200 mL daily (group A) or twice weekly (group B) and milk ad lib for 12 months.	100 % in both groups continued maintenance, similar frequency of allergic symptoms.	N/A	8/15 in group A and 9/15 in group B had recorded events.	$\downarrow$ milk IgE and milk SPT both groups after 12 months consumption.	RCT to compare maintenance frequency.
Martorell et al. 2011 [67]	60, 2–3.5 years	Fluid milk.	RCT, open label. (OIT/milk-free diet).	Clinical history, +SPT, milk, or CM protein IgE >0.35 kU/L, DBPCFC, anaphylaxis to milk excluded.	2 days, 0.01–2.5 mL, hourly.	Weekly in 15 increments to 200 mL, 16 weeks.	200 mL (6400 mg) daily, 12 months.	At 1 year, 90 % milk OIT tolerant to 200 mL daily, 13 % (3/23) of control passed DBPCFC. RR 7.7 for milk OIT vs. placebo.	N/A	80 % OIT patients had ≥ 1 reaction, all mild-moderate. Reactions with 15 % (114/738) doses.	$\downarrow$ milk IgE and milk SPT in OIT, but not control.	RCT with young patients.
Salimivasi et al. 2013 [68] Pasassilta et al. 2016 [69]	24, 6–14 years	Fluid milk	RCT, placebo control, double blind, open-label crossover.	History of anaphylaxis to CM or reaction within 6 months or +OFC, +milk SPT or milk IgE >3.5 kU/L.	None	1 drop of 1:25 dilution daily for 7 days, then increases every 1–3 days to 200 mL, 22 weeks. First dose and 8 others given in clinic.	200 mL (6400 mg) daily for 6–12 months.	89 % (16/18) OIT desensitized, not assessed in placebo. 100 % (10/10) control patients desensitized in crossover to open-label OIT. At 12 months, 13/18 (72 %) of OIT taking 6400 mg CM daily.	At 3 years, 85 % OIT (including original OIT and crossover) tolerating milk daily, 58 % at 7 years.	Desensitization: 100 % of OIT, 80 % crossover, 63 % of placebo patients reported milk daily, symptoms 6–12 months maintenance: 62 % had symptoms, none severe; 50 % at 3 years, 19 % at 7 years.	High baseline milk IgE predicted nonuse of milk products at 7-year follow-up—9.4 kU/L full tolerance, 24.5 kU/L partial or failed tolerance.	RCT, long-term outcomes.
Nadeau et al. 2011 [70]	11, 7–17 years	Powdered milk.	Open label, omalizumab for 16 weeks.	Clinical history, +milk IgE and SPT. Median milk IgE 50 kU/L.	1 day 0.1–1000 mg, increase every 30 min.	Weekly increase to 2000 mg for 7–11 weeks.	2000 mg daily for 8 weeks.	90 % reached maximum daily dose, also passed DBPCFC to	In progress.	Dose escalation: 1/11 had re-action requiring epinephrine.	N/A	Pilot study of OIT+omalizumab.

Table 2 (continued)

No. of patients, ages	Food allergen	Study design	Entry criteria	Initial dose escalation	Up-dosing	Maintenance phase	Desensitization results	Long term results	Adverse events	Laboratory results	Notable features	
Wood et al. 2015 [71••]	57, 7–32 years	Powdered milk	RCT, double blind, placebo controlled (omalizumab 16 months/s/placebo).	+SPT and DBPCFC ≥2 g milk. Life-threatening anaphylaxis or severe asthma excluded. Median milk IgE 42/38 kU/L omalizumab/placebo.	2 days: 0.07–9 mg, 8 doses. Biweekly increase to 520 mg or more, for 22–40 weeks.	520–3800 mg daily for 12 months. (omalizumab during up-dosing).	At month 28, 86 % omalizumab, 69 % placebo were desensitized (passed milk OFC). Shorter escalation phase with omalizumab (median 26 weeks, placebo 30 weeks).	Sustained tolerance: after milk OIT stopped for 8 weeks, 46 % omalizumab and 34 % placebo passed milk OFC.	Desensitization: reactions with 1.6 % (32/2199). Maintenance: 2 reactions requiring epinephrine at home.	Reactions with omalizumab in 8.5 % of doses, 26 % for placebo. Fewer doses requiring treatment and less severe reactions with omalizumab. ↓ milk SPT at end for both groups. After 16 months, ↑ casein IgG4, IgG, IgG4 ratios for both groups.	Reactions with omalizumab: casein IgE ↑ after 4 weeks treatment, ↓ at end. Placebo: milk and casein IgE ↓ after 4 weeks. ↓ milk SPT at end for both groups. After 16 months, ↑ casein IgG4, IgG, IgG4 ratios for both groups.	RCT of OIT+ omalizumab.
Goldberg et al. 2015 [72]	15, 6–12 years	Baked milk.	Open label, uncontrolled.	OFC for unheated (≤30 mg) and baked milk (reacted to <120 mg but ≥25 mg).	None. 50 % monthly increase under medical supervision.	Baked milk products daily as tolerated.	21 % tolerated 1.3 g baked milk OFC. Maximum tolerated dose 900 mg unheated milk.	N/A	8/15 did not complete desensitization due to IgE-mediated reactions. 2 had anaphylaxis requiring epinephrine with home doses.	↓ milk, casein, α-lactalbumin IgE in patients who reached maintenance dose. Responders also had modest difference in BAT to unheated milk vs. heated for 30 min.	OIT with baked milk.	

↓ means decreased; ↑ means increased

Table 3 Egg OIT studies

	No. of patients, ages	Food allergen	Study design	Entry criteria	Initial dose escalation	Up-dosing	Maintenance	Desensitization results	Long-term results	Adverse events	Laboratory results	Notable features
Patriarca et al. 2007 [42]	36 (17 egg, 10 control), 4–16 years.	Raw shaken (whole) egg.	Open label, unmatched controls (egg-free diet). (Multiple foods in same study).	DBPCFC for raw egg.	Sublingual then swallowed, daily increase from 1 to 10 drops 1:100 dilution, 24 days.	Every 3 days, 0.1–50 mL raw egg, 5–8 months.	1 egg at least 2–3 times/week (form/duration N/A).	71 % (10/14) of OIT completed desensitization to 50 mL raw whole egg, 7 % (1/14) partially desensitized, 100 % of control OIT due to failed DBPCFC.	N/A	For all foods: 30 % (11/36) of patients had side effects, 11 % of (4/36) patients discontinued OIT due to symptoms. All OIT patients had some symptoms; 20 % (4/20) of control had symptoms after stopping OIT for 2 months) vs. 35 % of controls.	↑ specific IgG4, ↓ specific IgE (for all foods, egg not separated).	Early OIT study, sublingual plus oral dosing in initial steps.
Staden et al. 2007 [44]	45 (11 egg, 10 egg avoidance control, 24 other foods), 0.6–12 years.	Lyophilized egg white.	RCT, open label (OIT/egg-free diet). (Both egg and milk in same study).	DBPCFC	N/A	Daily at home for 3–4 months, 0.006–2800 mg egg protein, median 7 months (all foods).	1600 mg egg daily plus deliberate intake, mean 9 months.	64 % (16/25) fully or partially desensitized (milk and egg OIT assessed jointly), 35 % of control later tolerant.	36 % of egg OIT had sustained tolerance (passed DBPCFC after stopping OIT for 2 months) vs. 35 % of controls.	↓ specific IgE in desensitized OIT patients and control patients tolerating food.	↓ specific IgE in desensitized OIT patients and control patients tolerating food.	RCT, sustained, unresponsive-ness
Morisset et al. 2007 [40]	84, 1–8 years.	Hard-boiled egg.	RCT (OIT/egg-free diet). (Both egg and milk in same study).	965 mg raw Negative food challenge to egg white. Mean egg IgE 3.8 kU/L.	N/A	3 months, up to 4 g egg yolk + white, home-based protocol.	Daily intake including creamy desserts and flan, 6 months total.	69 % OIT (32/49), 51 % (18/35) control patients desensitized and passed SBPCFC (7 g raw egg white).	N/A	N/A	↓ SPT and IgE in OIT vs. control.	More tolerant patients at baseline, use of cooked egg.
Buchanan et al. 2007 [32]	21 (initially 7), 1–16 years.	Dried egg white.	Open label, no control.	Clinical history of reaction, +egg SPT, egg IgE >7 kU/L (>2 if ≤2 years old), systemic anaphylaxis excluded.	1 day, 0.1–200 mg, 12 steps, total 399 mg. Last tolerated dose repeated next day.	Biweekly, 25–300 mg, increase by 25 or 50 mg.	300 mg daily, 24 months.	90 % of 21 reached 300 mg daily, 57 % of 7 initial patients passed DBPCFC for 8 g egg.	26 % of 7 had sustained unresponsive-ness (pass DBPCFC after stopping OIT 3–4 months).	Up-dosing: 1/7 initial patients reacted. Maintenance: no reactions in 7/7 patients, 3 had no reaction to accidental egg exposure.	↑ egg IgG, ↓ egg IgE in 5/7 patients, but not significant.	Pilot study, evaluation of SU
Vickery et al. 2010 [47]	8, 3–13 years.	Dried egg white.	Open label, no control (same protocol as [32], different patients).	Clinical history of reaction, +egg SPT, egg IgE >7 kU/L (>2 if <2 year old), systemic anaphylaxis or severe asthma excluded. Median egg IgE 12.5 kU/L.	1 day, 0.1–50 mg, 3.6 g (if egg IgE >2 U/L, dose increased by 600 mg every 4 months), median 174 days.	Biweekly to 0.3 or 300 mg daily, 34 months.	300 mg–3.6 g daily, median 34 months.	75 % (6/8) OIT reached maintenance. After 4 months, 62.5 % (5/5 tested) passed OFC to 3.9 g egg, 1 not tested. After median 34 months, 75 % (6/6 who reached maintenance) passed DBPCFC.	Sustained unresponsive-ness: After 1 month off OIT, 75 % (6/6) passed 2nd DBPCFC. All incorporated egg into diet.	Buildup: 4/6 who completed had reactions. Maintenance: no reactions requiring epinephrine.	↓ egg SPT and egg IgE, ↑ egg IgG4 but not significant. Egg specific CD4 ⁺ CD25 ^{hi} Tregs detected.	Individualized dose based on egg IgE levels.
Itoh et al. 2012 [37]	6, 7–12 years.	Scrambled egg.	Open label, no control.	Clinical history of severe anaphylaxis (grades 4–5) within 1 year, +egg IgE, +DBPCFC (median	Rush: every 30 min, 3–5 times daily. Egg white to 1 g then scrambled egg up to 60 g. (All dose increases in hospital.) Mean time 12 days.	Egg white to 1 g then scrambled egg twice weekly 9–12 months.	1 heated whole egg twice weekly 9–12 months.	100 % desensitized to 1 scrambled egg (60 g), mean time 12 days, 50 % also passed OFC 1 g powdered egg after 9–	16–21 months after rush desensitization, all continuing to eat 1 heated egg twice weekly.	100 % had allergic symptoms during desensitization. None required epinephrine.	↑ egg IgE during desensitization, then ↓ after ↑ egg IgG4 12 months after ↓ IL-10 and TGF-β1, no change in	Rush OIT protocol for cooked egg.

Table 3 (continued)

	No. of patients, ages	Food allergen	Study design	Entry criteria	Initial dose escalation	Up-dosing	Maintenance	Desensitization results	Long-term results	Adverse events	Laboratory results	Notable features
Garcia-Rodriguez et al. 2011 [36]	23, 5–17 years.	Raw and cooked egg.	Open label, no control.	threshold 152 mg). Clinical history and +SPT, +IgE, or OFC. Unstable respiratory status excluded.	Rush: 0.13–1060 mg egg white, then half cooked egg. Median 11 days.	Slow protocol if symptomatic (60–90 days).	1 cooked egg daily for 3 months, then every 2–3 days for 12 months.	12 months maintenance. 87 % (20/23) OIT desensitized (tolerated 1 cooked egg), 61 % (14/23) desensitized within 5 days.	2 patients (9 %) who failed initial desensitization switched to slow protocol, desensitized in 60–80 days.	78 % (18/23) had allergic reaction during desensitization. Total reactions 55, 35 mild and 20 moderate. 2 patients had reactions during daily cooked egg maintenance.	IL-4 and IFN- γ . ↓ egg IgE, SPT, ↑ egg IgG at 6 months vs. baseline.	Trial of fast rush (cluster) desensitization.
Tortajada et al. 2012 [45]	19, 3–14 years.	Raw egg.	Open label, prospective, no control.	Clinical history, +egg SPT, OFC.	No rush.	Weekly, 0.5 mg–30 g, 16 weeks.	0.5 egg twice weekly for several months, then 1 egg weekly.	89 % (17/19) desensitized to 30 g, no control.	N/A	2/19 had anaphylactic reactions requiring epinephrine, discontinued OIT.	N/A	Low maintenance frequency.
Burks, et al. 2012 [74••]	55, 5–11 years.	Dried egg white.	RCT, placebo controlled, double blind (OIT/placebo).	Clinical history of reaction, egg IgE >5 kU/L (≥6 years old) or >12 (<6 years old), severe anaphylaxis excluded. Median egg IgE 1095 kU/L in OIT, 1061 kU/L in control.	1 day, to maximum 50 mg.	Biweekly, doubled every 2 weeks to 50 mg (if max dose not reached initially), then by 25 % up to 2 g.	2 g daily (approx 1/3 egg), 10 months.	At 10 months, 55 % on OIT, 0 % on placebo desensitized (OFC 5 g). At 22 months, 75 % on OIT desensitized (OFC 10 g).	Sustained unresponsiveness: at 24 months, after off egg for 4–6 weeks, 27.5 % OIT passed 10 g OFC, Not tested in placebo.	Desensitization: adverse events with 25 % of 11,680 OIT doses, 4 % 4018 placebo doses. No adverse events in patients with SU consuming egg ad lib.	OIT patients had ↓ egg SPT, ↓ egg BAT, ↑ egg IgG4, no change in egg IgG vs. placebo patients.	RCT, evaluation of SU after egg OIT.
Ojeda et al., 2012 [41]	31, 6–15 years.	Raw egg.	Open label, controlled (not randomized).	Clinical history, egg SPT, and/or +egg IgE, +OFC to 1 boiled or unpasteurized egg.	No rush, first treatment dose in clinic.	Daily increases at home, 0.151 mg–6 g (50 mL), median 43 days.	0.5 raw (pasteurized) egg 3 times weekly.	81 % (25/31) in OIT reached maximum dose, 74 % passed OFC for 1 unpasteurized egg, 3 % partially desensitized, 10 % not desensitized but increased reactivity threshold. Control outcomes N/A.	N/A	74 % of OIT patients reacted. 180 adverse events, 86 were grades 1–2, 4 required epinephrine at home.	ELISA: unpasteurized egg extract 4 times more allergenic than pasteurized egg, but all patients desensitized to pasteurized egg also passed OFC to unpasteurized egg.	OIT in patients tolerating cooked but not raw egg, comparison to unpasteurized egg.
Ruiz-Garcia et al. 2012 [43]	17, 6–38 years.	Dried egg white—OVODES NM kit.	Open label, not controlled.	Clinical history, +egg SPT, +egg IgE, OFC to dried or raw egg within 3 months.	Initial dose in hospital.	Weekly 4–3600 mg, 9 steps, mean 7 weeks.	3 eggs per week, 9 months.	82 % (14/17) reached maintenance dose and tolerated for 9 months.	N/A	70.5 % (12/17) symptomatic during OIT, 3 required epinephrine during up-	Post-OIT total and egg IgE reported but not analyzed.	Use of commercial product for OFC and desensitization.

Table 3 (continued)

	No. of patients, ages	Food allergen	Study design	Entry criteria	Initial dose escalation	Up-dosing	Maintenance	Desensitization results	Long-term results	Adverse events	Laboratory results	Notable features
Letran et al. 2012 [38]	17, 4–14 years.	Raw egg.	Open label, not controlled.	Median egg IgE 3.6 kU/L. Clinical history, OFC (75 %), or recent clinical reaction. Anaphylaxis within 6 months, severe asthma or severe atopic dermatitis excluded.	Raw egg diluted in yogurt, double dose every 20 min.	Monthly in hospital, 1/65-1 egg interval and steps NR.	1 egg omelet (or fraction tolerated), frequency NR.	35 % (6–17) fully desensitized.	N/A	Up-dosing: 4 reactions reported. Maintenance: 47 % (8/17) had mild symptoms, 1 patient required emergency room visit.	Post-OIT total and egg IgE reported but not analyzed.	Cooked egg for maintenance after raw egg desensitization.
Meglio, et al. 2013 [39]	20, 4–14 years.	Raw egg.	RCT, open label (OIT/egg-free diet)	+Egg SPT and IgE >0.35 kU/L, DBPCFC (80 %) or clinical history. Median OVA IgE 11.3 kU/L OIT, 10.5 kU/L control.	No rush, first dose in hospital.	Daily increases 0.27 mg–13.6 g (25 mL), 181 days.	Raw egg 3 times/week or food with 3 eggs weekly, 6 months.	80 % (8/10) OIT, 0 % control tolerated 25 mL (13.6 g) daily; 10 % OIT had partial tolerance.	N/A	7/10 OIT had some symptoms during desensitization, 5 resolved, 1 tolerated limited amounts, 1 discontinued.	OIT: ↓ ovomucoid and OVA IgE, (ISAC method but not with REAST). No change in control.	Randomized comparison of OIT for desensitization.
Della Iacono, et al. 2013 [34]	20, 5–11 years.	Raw egg.	RCT, open label (OIT/egg free diet)	Clinical history of anaphylaxis, +egg SPT, and IgE, DBPCFC <0.9 mL raw egg. Poorly controlled asthma excluded.	No rush, first dose, and 5 doubling doses monthly in clinic.	In clinic doubling monthly, plus home increases, 37 steps, 176 days.	10–40 mL egg daily.	After 6 months, 0 % (0/10) in egg OIT desensitized to 1 raw egg (40 mL); 90 % partially desensitized (tolerated 10–40 mL), 0 % control passed DBPCFC.	N/A	100 % OIT patients had 53 total adverse events during desensitization. 24 % were grades 1–2. None required epinephrine, 30 % control patients had 5 total adverse reactions from accidental egg ingestion.	OIT: ↓ egg SPT and egg IgE, no change in control.	Severe egg allergy, home-based protocol.
Fuentes-Aparicio et al., 2013 [35]	72, 5–15 years.	Dried egg white.	RCT, open label (OIT/egg-free diet).	Clinical history, +egg SPT and egg IgE, OFC if no reaction within 2 months prior to study. Mean egg IgE 9 kU/L OIT, 9.3 kU/L control.	2 days, 1–30 mg.	Weekly to 10 g (mean 70 days).	10 g daily for 1–6 months.	After 1 month: 92 % (37/40) OIT, 22 % (7/32) control desensitized to or tolerated egg.	54 % (20/37) OIT passed OFC to 10 g raw egg and introduced into diet.	Desensitization: 21/37 had symptoms, 5 reactions required epinephrine. 1 patient withdrew with eosinophilic esophagitis.	↓ egg SPT, egg IgG in OIT patients. No significant differences in egg IgE.	RCT
Vazquez-Ortiz et al. 2014 [46]	82, mean 8.3.	Raw egg.	Non-randomized, controlled, open label. (Parallel OIT/avoidance).	+Egg SPT and IgE; positive DBPCFC to 1 boiled egg; if negative, then FC to raw egg. Median egg IgE 6.44 kU/L.	3 days, hourly, 0.001–0.4 mL.	Weekly 0.05–60 mL (1 egg), median 4.5 months.	1 egg twice weekly, median 11 months.	Desensitization: 80 % (40/50) OIT reached 2 eggs/week.	At 12 months of maintenance, 56 % (28/50) OIT passed OFC for 1 raw egg, 8 % (4/50) of OIT partially	Dose-related reactions in 45/50 (90 %) and 7.6 % (102/4) DBPCFC. 13,551 of egg-OIT doses, 61 %	Risk factors for reaction: asthma, IgE >8, early reaction in DBPCFC. Lower egg and OVA IgE	Evaluation for risk factors for reaction to OIT.

Table 3 (continued)

No. of patients, ages	Food allergen	Study design	Entry criteria	Initial dose escalation	Up-dosing	Maintenance	Desensitization results	Long-term results	Adverse events	Laboratory results	Notable features
Caminiti et al. 2015 [33]	Dried egg white.	RCT, placebo control, double blind (OIT/placebo).	Clinical history, +egg SPT, +egg IgE, DBPCFC. None had consumed baked egg. Median egg IgE 36.6 kU/L OIT, 38.4 kU/L control.	No rush.	0.1–4000 mg weekly, 4 months.	1 cooked egg twice weekly, 6 months.	94 % (16/17) OIT, 0 % control (0/14) desensitized (passed DBPCFC 4 g).	After 6 months of egg diet then 3 months avoidance, 29 % (5/17) OIT, 7 % (1/14) placebo had sustained tolerance (DBPCFC).	Desensitization: 3 patients had adverse events, 1 discontinued OIT. Egg containing diet phase: 2 patients had symptoms.	Egg IgG ₄ OIT > placebo. o. No significant change in egg IgE either group. Egg IgG ₄ in SU patients > those who lost desensitization.	at baseline associated with later tolerance.
Escudero et al. 2015 [75]	Dried egg white.	RCT, open label (OIT/egg avoidance).	Clinical history, +egg SPT, egg IgE ≥ 0.7 kU/L, and DBPCFC. Severe anaphylaxis excluded. Median egg IgE 6.4 kU/L in OIT, 2.2 kU/L control.	1 day, 0.08–140 mg in 12 intervals, total 280 mg.	Weekly to 2808 mg, 9 intervals, median 32 days.	1 undercooked egg every 2 days and egg ad lib for 3 months, then off OIT 1 month.	93 % (28/30) on OIT desensitized. At 4 months, 37 % OIT passed DBPCFC. 2808 mg (11/25 control passed DBPCFC (1/31 challenged).	After 1 month avoidance, 37 % OIT, 3 % control had sustained unresponsiveness (DBPCFC 2808 mg).	145 reactions in OIT, 14 % in dose escalation, 54 % in buildup, 31 % in maintenance. 70 % of patients had ≥ 1 reaction, 1 required epinephrine.	At 4 months, OIT patients had ↓ egg, ovalbumin and ovomucoid SPT and IgE, ↑ egg IgG ₄ .	Evaluation of SU.
Leonard et al. 2012 [76]	Baked egg.	Prospective, historical control.	Clinical history, OFC to unbaked egg, +SPT and +egg IgE (higher if no recent reaction), and tolerated baked egg in OFC (2.2 g).	N/A	N/A	1–3 servings of baked egg daily, 6 months.	53 % (42/70) tolerated partially cooked egg (OFC 6.5 g), 36 % (28/70) did not but continued baked egg.	Retrospective: 28 % (13/47) partially cooked eggs, 13 % (6/47) to baked eggs, 59 % (28/47) avoidant.	No reactions to baked egg consumption, 1 patient reacted to accidental exposure to unbaked egg.	OIT patients who became tolerant to unbaked egg: ↓ egg SPT; ↓ egg, ovalbumin and ovomucoid IgE; ↑ egg, ovalbumin and ovomucoid IgG ₄ .	Baked egg OIT to induce tolerance to other forms.

↓ means decreased; ↑ means increased

Table 4 Other OIT studies

No. of patients, ages	Food allergen	Study design	Entry criteria	Initial dose escalation	Up-dosing	Maintenance	Desensitization results	Long-term results	Adverse events	Laboratory results	Notable features
Rodriguez del Rio et al. 2014 [49]	Wheat porridge or pasta.	Open label, no control.	Clinical history of reaction, wheat IgE >0.35 kU/L, DBPCFC. Severe asthma excluded. Median wheat IgE 47.5 kU/L.	No rush.	Twice weekly, 0.0005 to 13 g, 21 days.	100 g daily, 6 months.	83 % (5/6) completed maintenance, 80 % also tolerant of oat.	N/A	Up-dosing: 6 adverse reactions in 2 patients (6.25 %, 6/96 doses). Maintenance: 1 patient had exercise-induced symptoms.	↓ wheat SPT and IgE at 6 months, but not statistically significant.	First large trial of wheat OIT.
Sato et al. 2015 [50]	Wheat noodles.	Open label, historical controls.	History of anaphylaxis confirmed on DBPCFC <1.3 g (baked wheat flour). Poorly controlled asthma or atopic dermatitis excluded. Median wheat IgE >100 kU/L.	Twice daily, 0.5–5.2 g (or max tolerated), 10 steps.	Weekly at home, 20 steps, 0.26–5.2 g.	5.2 g daily, 3 months.	89 % reached maintenance and tolerating 5.2 g daily.	After 2 years off OIT, 61 % passed OFC, 9.1 % in historical control.	Rush/dose escalation: 26 % (42/143) doses resulted in symptoms, none required epinephrine. Maintenance: 6.8 % (486/5778) doses with symptoms, 1 required epinephrine.	At 2 years, ↓ wheat IgE in OIT, no change in control. No difference in wheat IgE between tolerant and allergic patients in OIT group.	Trial of wheat OIT, evaluation of SU.
Begin et al. 2014 [52]	Peanut alone, or up to 5 foods simultaneously.	Open label, prospective control. (OIT for peanut + others or peanut alone).	SPT >7 mm, peanut IgE >2 kU/L, DBPCFC for 182 mg for each food (peanut, tree nuts, sesame, milk, egg).	1 day, 0.1–6 mg total (divided equally by food).	Biweekly, 28 weeks, to 20 g total (4 g for peanut).	4 g each allergen daily.	Clinical endpoints not reported but 12 % (3/25) multi-OIT and 20 % (3/15) peanut OIT only patients discontinued due to noncompliance, change of residence, or unable to complete.	Multi-OIT—longer time to maximum doses than peanut OIT. Long-term study in progress.	No significant difference in reaction rates between peanut only or multi-OIT. Escalation: 60 % multi-OIT patients, 40 % peanut only. Up-dosing: 3.4 % multi, 3.7 % peanut. Home: 3.1 % multi, 2.9 % peanut.	After 1 year, no change in peanut IgE, ↑ peanut IgG4 in both groups.	Trial of multiple food OIT.
Begin et al. 2014 [77]	Peanut alone, or up to 5 foods simultaneously.	Open label, no control, omalizumab for all patients 9 weeks prior to start of OIT until maintenance dose reached.	+SPT, +food IgE, DBPCFC for each food (peanut, tree nuts, sesame, milk, egg, grains). Severe anaphylaxis or poorly controlled asthma excluded.	1 day, 5–1250 mg total (divided equally by food).	Biweekly, 10 steps, to 20 g total (4 g each allergen).	4 g each allergen daily.	All reached maintenance in 7–36 weeks; mean time to maintenance dose was 67 weeks earlier than in study w/o omalizumab.	In progress.	Escalation: 52 % of 25 reacted, all grade 1. Up-dosing: 5.7 % of 2227 doses, all grade 1. Maintenance: 5.3 % of 7530 doses. 1 patient required epinephrine.	At 52 weeks, no significant change in peanut IgE, ↓ peanut SPT, ↑ peanut IgG4.	Trial of rush protocol, multiple food OIT with omalizumab.

↓ means decreased; ↑ means increased

completed the study. After discontinuing OIT for 4 weeks, 12/39 patients (31 %) tolerated 5000 mg of peanut protein and an open oral feeding of peanut butter and were considered to have successfully achieved SU. Interestingly, for the other 12 who did not, a median cumulative dose of 3750 mg was required to elicit symptoms during the DBPCFC. At baseline and the time of challenge, subjects who achieved SU had smaller skin test results, as well as lower peanut-s-IgE, Ara h 1, and Ara h 2 level and lower ratios of peanut-specific IgE/total IgE compared with subjects not passing. Peanut-IgG4 levels were not predictive of SU.

Another open-label study evaluated rush peanut OIT [22]. Twenty-three pediatric patients who reacted to up to 1 g of peanut protein in a DBPCFC received OIT with crushed roasted peanuts. Rush escalation was performed two to four times per day over 7 days, to a maximum dose of 500 mg peanut, or double the maximum tolerated dose from the DBPCFC. In most patients, the amount of peanut tolerated during rush desensitization was not different than the eliciting dose in DBPCFC. There was a significant inverse correlation between the level of peanut-s-IgE and the amount of peanut tolerated using the rush protocol. For up-dosing, if 500 mg peanut was not reached during rush desensitization, the dose was increased by approximately 20 % every 2–4 weeks for up to 20 months. Sixty-one percent of patients (14/23) reached the maintenance dose of at least 500 mg peanut and remained on it for a median of 8 weeks (range 7–13 weeks). They were then taken off OIT for 2 weeks and underwent an exit DBPCFC. Only eight patients (34 %) tolerated a dose higher than the maintenance during exit DBPCFC (median increase 0.5 g peanut).

The first double-blind, placebo-controlled RCT of peanut OIT was reported in 2011 [27•]. In this multicenter study, 28 pediatric patients with a history of peanut allergy were randomized in a 2:1 ratio to receive OIT with defatted peanut flour or placebo. Unlike prior studies [24], the initial day 1 dose escalation was limited to a maximum of cumulative dose of 12 mg followed by buildup biweekly for 44 weeks up to 4000 mg daily. Eighty-four percent of patients on OIT (16/19) reached the goal maintenance dose and passed the exit DBPCFC (5000 mg peanut protein), while the placebo patients tolerated a median cumulative dose of 280 mg (range 0–1900 mg).

The largest peanut OIT study to date was performed in the UK, and 99 children who failed a DBPCFC at ≤ 100 mg peanut protein were randomized to receive peanut OIT or peanut avoidance in the first part of the trial, followed by peanut OIT in the second part [55••]. Patients with a history of life-threatening peanut allergy or severe asthma were *not excluded*. Slow up-dosing started at 0.5 mg and continued every 2 weeks until 800 mg was reached. Patients remained on 800 mg peanut daily for 26 weeks, followed by a DBPCFC up to 1400 mg protein, after which control patients crossed

over in active OIT phase II, following the same OIT protocol. DBPCFC was passed in 62 % of the active group and 54 % of controls. QoL measured in patients 7–12 years improved after treatment in both groups. Mild adverse events occurred in 6.3 % of doses. Wheezing occurred in 0.41 % of 22 participants and was treated with β_2 -agonist and antihistamines, except for one patient who additionally self-administered epinephrine on two separate occasions.

A more recent US multi-site study has evaluated the use of AR101, a pharmaceutical formulation of defatted peanut flour in a double-blind, placebo RCT [81]. Fifty-five patients (4–21 years old), who failed a DPBCFC at ≥ 100 mg peanut protein, received biweekly up-dosing up to 300 mg peanut protein daily. Seventy-nine percent of AR101 patients passed an exit DBPCFC (443 mg cumulative peanut protein), compared to 19 % of placebo patients. GI symptoms were the most common adverse events and were noted in 72 % of active participants and 27 % of placebo. A single dose of epinephrine was administered during OIT (*manuscript in preparation*). A long-term follow-up study of these patients as well as a large international phase III study is in progress.

Omalizumab as an Adjunct to Peanut OIT

Anti-IgE therapy was shown to significantly increase the threshold of reactivity in peanut-allergic patients [82]. In a phase I pilot open-label study, we have evaluated the use of omalizumab (monoclonal anti-IgE antibody) as an adjunct therapy to peanut OIT [58]. Thirteen patients with highly elevated peanut-s-IgE who failed a DBPCFC at ≤ 50 mg peanut protein received omalizumab every 2–4 weeks until week 12, when they underwent successfully a rapid 1-day escalation up to a cumulative dose of 496 mg protein. Weekly up-dosing up to 2000 mg protein was performed over a median of 8 weeks, after which omalizumab was discontinued. Patients continued 2000 mg maintenance dosing daily for 12 weeks, then underwent another DBPCFC, up to 4000 mg of peanut protein. Eighty-five percent of patients passed DBPCFC at 4000 mg. Compared to prior trials without omalizumab, these patients were able to tolerate high maintenance doses of peanut in shorter periods of time (median dose 8 weeks of OIT) with less adverse reactions during rush escalation day. Another open-label clinical study of omalizumab with peanut OIT also reported decreased side effects during dose escalation [78]. A larger multi-site, double-blind, randomized, placebo-controlled study of omalizumab in patients with significant peanut allergy is ongoing [83].

Probiotic as an Adjunct to Peanut OIT

A double-blind placebo-controlled RCT has suggested that the use of probiotic bacteria in combination with peanut OIT may lead to a better rate of SU [60]. Sixty-two patients with

history of clinical reaction to peanut were randomized to receive either peanut OIT/*Lactobacillus rhamnosus*, or placebo/placebo. After 18 months, therapy was discontinued. SU was assessed after ≥ 2 weeks later. Eighty-two percent of patients on OIT/probiotic tolerated a DBPCFC, in contrast to 3 % of placebo patients. Limitation of the study included lack of peanut OIT/placebo arm and an earlier evaluation of SU (≥ 2 weeks, compared to ≥ 4 weeks).

Cow's Milk OIT

After initial report of OIT to different foods including cow's milk (CM) in 1985 [84], in 2004, a small pilot, open-label study [30] described OIT in 21 CM-allergic children (5–10 years old), with a history of severe CM allergy or a positive DBPCFC at ≤ 162.5 mL milk. Patients received CM up-dosing every 1 week starting from 1 drop diluted milk (1:25) until 4 mL weekly in clinic then at home. Desensitization to 200 mL CM was successful in 71 % of patients. On follow-up after 4–5 years, 67 % of patients remained desensitized [61].

A larger open-label RCT compared CM OIT to CM avoidance in patients with more severe milk allergy [29]. Sixty patients, ages 4–10 years, with history of at least one severe allergic reaction to milk and very high milk serum-specific IgE levels (>85 kU/L), who failed DBPCFC at ≤ 0.8 mL CM, were randomized to CM OIT or CM-free diet. Dose escalation was performed on an inpatient basis over 10 days several times per day to a maximum of 20 mL CM. Home up-dosing then occurred every other day to a goal of 150 mL daily for 1 year. Patients tolerating 150 mL milk were allowed to liberalize the daily intake to include dairy products. Of patients in the OIT arm, 36 % completed the full desensitization and tolerated 150 mL milk daily. In comparison, all patients in the control group reacted to <150 mL milk during DBPCFC. Hence, as with peanut OIT, CM rush desensitization appeared to be less effective, although these results may also have been at least partly secondary to the extreme CM sensitivity of the patients.

A placebo-controlled, double-blind RCT CM OIT open-label follow-up [31, 62, 63••] enrolled older patients from the USA. In the initial study [31], 20 patients (6–21 years old), who reacted to ≤ 1340 mg CM in a DBPCFC, were randomized to receive CM OIT or placebo. Dose escalation with milk powder was performed as a single day rapid escalation/build up from 0.4 to 50 mg. Dose increases then occurred weekly or biweekly over 8 weeks to a goal of 500 mg (equivalent to 15 mL of CM), after which patients continued to receive daily maintenance doses for 13 weeks. Desensitization was tested at the conclusion of OIT maintenance (or placebo) by another DBPCFC up to 8000 mg cumulative dose, which was significantly higher than the daily

maintenance dose used in the study. The median change in milk dose threshold was 5100 mg in OIT group ($p < 0.002$), with no change in the median in the placebo group. Four OIT patients tolerated a cumulative dose of 8000 mg with mild or no symptoms [31]. Despite the relatively high frequency of reactions of any type (45 % of active doses), nearly 90 % were transient reactions that required no treatment. Approximately 1:100 active doses resulted in a multisystem reaction, and 1:600 resulted in a reaction necessitating epinephrine therapy. Possible explanations for this rate of reactions included that subjects may have been more severely allergic, who were more diligent in reporting symptoms, and were not taking maintenance oral antihistamines as in some studies, in addition to different criteria for using epinephrine between sites or countries.

In follow-up, patients tolerating at least 2540 mg of CM were maintained on open-label milk OIT for 3–17 months and had home escalation up to a median of 7000 mg milk protein, followed by a third DBPCFC up to 16,000 mg CM protein [62]. Of these patients, 6/15 (46 %) tolerated a significantly higher dose of CM protein (16,000 mg), while 53 % reacted at a level of 3000–16,000 mg. A very important longer-term follow-up study for these patients [63••] also included a total of 32 patients from this and another study [28]. At 5 years on OIT, 19 % reported unlimited consumption of milk, 31 % were taking at least one serving a day, 34 % were taking more limited amounts, and 16 % were now avoiding milk [63••]. Twenty-two percent reported limiting their consumptions because of anxiety (9 %) or taste (13 %). Interestingly, some subjects who initially did well, and passed prior food challenges, subsequently had increased symptoms and began to restrict milk. Hence, patients appeared to lose their desensitization status over time.

Another randomized, open-label study of CM OIT or CM-free diet in 60 younger children (24–36 months) followed a 2-day rush escalation from 1-mL diluted CM (1:100) to 12-mL undiluted milk [67]. Patients were up-dosed weekly over 16 weeks until 200 mL maintenance was reached. After 12 months, 90 % of milk OIT patients were tolerating 200 mL, compared to 23 % of control patients on milk-free diet. This was a higher rate of desensitization than other studies, possibly indicating that OIT in the younger age group may be more successful.

A placebo-controlled RCT performed in children (6–14 years old) [68, 69•] followed patients for up to 7 years. Twenty-eight patients reactive to CM on DBPCFC were randomized to CM OIT or placebo at a 2:1 ratio. Patients receiving placebo were offered open-label crossover after 6 months. The up-dosing occurred weekly from 1 drop of milk to 200 mL, initially in the hospital and later at home, over 22 weeks. Eighty-eight percent of patients were tolerating CM at 6–12 months, compared to 85 % after 3 years of OIT. At 7 years, only 50 % (14/28) were taking CM or

CM product daily (≥ 6400 mg protein), similar to rates reported by Keet et al. [63••]. Interestingly, CM-related symptoms decreased from 50 to 19 % of patients at 3 and 7 years, respectively.

In a Cochrane meta-analysis from 2012 that comprised 106 patients on CM OIT [85], adverse reactions were seen in 92 % of subjects, although they were mostly local and mild. The majority (82 %) of the adverse reactions took place during the escalation period, and 40 % took place during the long-term follow-up period.

Baked Milk OIT

A recent open-label study tested baked milk (BM) OIT in baked milk-reactive patients [72]. Only 21 % of patients completed the 12-month protocol and tolerated 1300 mg BM in an OFC. Fifty-seven percent did not complete the program because of adverse reactions, which were experienced by 86 % of patients.

Omalizumab as an Adjunct to Milk OIT

A small open-label study using omalizumab as an adjunctive treatment to milk OIT suggested that this approach can lead to a faster desensitization with lesser adverse reactions [70]. Mean frequency of total reactions was 1.6 %, although the rate of epinephrine administration was similar to prior studies.

In a recent double-blind, placebo-controlled RCT [71••], 57 subjects (age 7–32 years) were randomized to receive omalizumab or placebo, after failing a DBPCFC to ≤ 2 g milk protein. Open-label milk OIT was initiated after 4 months of omalizumab/placebo, beginning with 2-day dose escalation from 0.07 to 9 mg, then up-dosing biweekly for 22–40 weeks up to 520–3800 mg CM protein. At 12 month of OIT, patients were un-blinded; those who were in the active group continued omalizumab until month 28, when anti-IgE was discontinued. All patients then underwent DBPCFC up to a cumulative dose of 10 g milk protein. Patients passing the challenge continued maintenance for 8 more weeks, then stopped for another 8 weeks (month 32), and underwent a final DBPCFC to evaluate for SU. Patients on omalizumab had a shorter up-dosing phase secondary to fewer reactions (91 % of symptom-free doses in active group compared to 73.9 % in placebo). At month 28, 89 % of omalizumab-treated subjects and 71 % of placebo-treated subjects tolerated 10 g of CM in DBPCFC. At month 32, no significant difference was found in SU in patients in the active group (48 %) compared to placebo (36 %). This study therefore provided further evidence that the use of omalizumab decreases the rate of allergic reactions during up-dosing. However, it did not lead to a better rate of SU.

Hen's Egg OIT

Over the past two decades, clinical studies of hen's egg OIT have spanned a broad range of designs, with significant variations in protocols. In an excellent recent review, Ibanez and colleagues have reviewed the different egg OIT studies and highlighted their heterogeneity [86•]. For example, while some studies have used raw egg [39, 42], most have used a modified form of egg, such as pasteurized whole egg [41], pasteurized raw egg white [46], lyophilized egg white [44], dehydrated whole egg [35], dehydrated egg white [32, 33, 74••, 75], or cooked forms like boiled egg [40], scrambled egg [37], or omelet [36]. Protocols that effectively desensitized egg-allergic patients to hard-boiled egg were less efficacious at inducing desensitization to raw products [40]. There are also size variations between different eggs, leading to differences in protein content per egg. Comparison of equivalence between protocols is therefore very extremely difficult, especially that not all protocols have expressed the doses of egg protein per se. In addition, most studies had an open-label, uncontrolled design [86•]. A 2014 Cochrane review of 87 papers led to the analysis of four randomized controlled trials, three of which had control group practicing egg avoidance and one had a placebo group [87•]. Here, we will discuss in more detail the RCTs that illustrate the variability of egg OIT protocols.

Burks and colleagues conducted a double-blind, placebo-controlled multi-site RCT [74••], in which 55 patients, ages 5–18 years, with a history of egg allergy and elevated egg-s-IgE were enrolled and randomized at an 8:3 ratio to receive egg OIT or placebo. Patients underwent a 1-day escalation and build up to a 2-g maintenance dose. At 10 months, 55 % of OIT patients and 0 % of placebo passed a DBPCFC to a cumulative 5 g of egg powder. Patients were then un-blinded, and placebo patients practiced egg avoidance. At 22 months, 75 % of OIT patients tolerated 10-g cumulative of egg powder, even though the challenge dose was twice as high. However, the majority of placebo patients did not undergo this DBPCFC per protocol, as their egg-s-IgE was >2 kU/L. Egg OIT was discontinued for 4–6 weeks, after which only 27.5 % were found to have SU during a third DBPCFC of 10 g, followed an hour later by a whole cooked egg. Hence, as in peanut studies, SU could be achieved by only a minority after 2 years of egg OIT.

Dello Iacono and colleagues [34] enrolled 20 children (ages 5–11 years) with a history of anaphylaxis grade 3 or higher within prior 12 months, positive egg-s-IgE, who had a dose-eliciting reaction during OFC to ≤ 0.9 mL raw egg emulsion. Patients were randomized at a 1:1 ratio to raw egg OIT or avoidance. OIT started at 1 drop and aimed for 40 mL maintenance (about equivalent to a small egg). Most up-dosing occurred at home, over 176 days and 32 steps. No patient achieved full desensitization, but 90 %

were partially desensitized (maintenance dose between 5 and 40 mL). All children in the OIT group had adverse reactions but none of them needed epinephrine, despite their clinical history.

Another randomized, open-label trial of raw egg OIT [39] used a different OIT protocol with 181 daily increases from 1 diluted drop (0.27 mg) to a maximum of 25 ml (13.6 g) raw egg prepared at home. Cetirizine was given daily until the end of the protocol. Of ten patients on egg OIT, 80 % reached the full maintenance dose while only two control patients reached tolerance spontaneously.

In a large, open-label RCT [35], 72 patients (4–15 years) were randomized to rush OIT with powdered pasteurized egg or to egg elimination diet, after reacting during DBPCFC. The 40 OIT patients underwent 2-day rush escalation up to 30 mg, then weekly up-dosing in clinic over an average of 10 weeks, towards a goal of 10 g of dehydrated whole egg. 92.5 % of patients in the OIT group achieved daily tolerance to 10 g egg, versus 21.8 % of control patients. Subsequently, at 6 months, 50 % of OIT patients and 22 % of controls passed another OFC to raw egg. 52.5 % of OIT patients developed adverse events. Of these, 38 % had mild and 61.9 % had more severe reactions. 12.5 % of patients required epinephrine.

In a more recent double-blind, placebo-controlled RCT designed to evaluate for SU, 31 children with egg reactivity on DBPCFC (median dose <139 mg) were randomized to dehydrated egg white OIT or placebo [33]. Weekly up-dosing from 0.1 to 4000 mg was performed over 4 months. Of OIT patients, 94 % reached 4000 mg, compared to none of placebo patients. Desensitized patients then ate one cooked egg twice weekly for 6 months, then stopped egg ingestion. After 3 months of egg avoidance, only 31 % of the active OIT patients had SU and passed the final DBPCFC compared to 7 % of placebo.

Similar results were obtained in a separate, open-label RCT [75]. Following reactivity to 2808 mg egg or less on DBPCFC, 61 patients (age 5–17 years) were randomized to receive OIT with dehydrated egg white, or dietary avoidance. After an escalation day up to 140 mg, rapid up-dosing to 2808 mg was achieved within a mean of 32 days. Of egg OIT patients, 93 % were desensitized to 2808 mg egg and progressed to eating at least one undercooked egg every other day in addition to baked egg ad libitum. Three months into OIT, they avoided egg completely for a month followed by another DBPCFC and continued OIT for a total of 3 months, then avoided egg for a week. SU was demonstrated by 37 % of OIT patients, while only 3 % of control patients passed the challenge. Seventy percent of OIT patients developed reactions (5.9 % of all doses), but none were severe. Only one dose of epinephrine was given during up-dosing. Elevated egg-s-IgE was associated with more adverse reactions.

Discussion

“When I have finally decided that a result is worth getting, I go ahead on it and make trial after trial until it comes.” –Thomas Edison

... Is OIT “worth getting”?

As illustrated above, while trials of OIT have increased our understanding of OIT, they have varied greatly in methodology, patient population, goals, and outcomes. A rigorous comparison of the outcome of these studies is therefore very difficult, if not impossible, since variability is noted in major components of the trials including the type of food used (raw, natural, modified, baked), inclusion/exclusion of patients with a history of severe allergies, the definition of a “severe allergy,” age of the patients, performance of an entry DBPCFC, and its dose-limiting criteria, as well as the duration and target dose of escalation, up-dosing, and maintenance phases. Importantly, rates of adverse reactions during OIT have varied considerably. This may be in part be due to variations in protocols, but also because of the heterogeneity in assessing and grading reactions, and variations in allergic sensitivity among patients. While rates of epinephrine administration have been compared among protocols, requirement for epinephrine is not always indicative of the severity of allergic reactions, as its indications for its use may vary in between sites or countries.

It is very challenging to draw solid conclusions comparing the different food-specific OIT protocols, but some patterns have been consistent. Several studies have shown that rush OIT is associated with lesser efficacy and more adverse reactions than slower OIT protocol, unless omalizumab is used. However, omalizumab is expensive, requires injections, and exposes patients to potential drug-related side effects. In addition, the effect of this approach on OIT reactions once omalizumab is discontinued is still under evaluation. Patients with a history of more significant clinical reactions (high-grade anaphylaxis) and/or elevated food-s-IgE, appear to be at increased risk of reactions during OIT, decreased probability of completing desensitization, and lower likelihood of developing SU [21, 22, 29, 34, 54••]. In addition, OIT safety and efficacy may be dependent on the age of the patients, and some studies have suggested that desensitization in younger children may be associated with better outcomes [67]. The relatively high rate of spontaneous resolution of some food including egg and milk allergy must be accounted for in OIT studies. Large RCTs are needed to evaluate whether early implementation of OIT may accelerate the development of tolerance.

Furthermore, the optimal minimal maintenance dose for each food remains to be evaluated. Lower maintenance doses may lead to a better compliance rate, but higher doses may

provide better protection from accidental ingestion, while allowing for ingestion of products that may contain traces of food allergen. Whether higher maintenance doses are superior to lower ones in achieving a better rate of SU requires further evaluation.

While clinical history and laboratory evaluation can identify patients at greater risk of allergic reactions, as yet there is no truly effective method to predict which patients can be successfully desensitized, who can maintain desensitization, and who may achieve SU. Current understanding of the mechanisms by which desensitization and SU operate is very scarce. The mechanisms may include mast cell and basophil suppression, development of food-specific IgG antibodies, reduction in the food-specific IgE/IgG4 ratio, up-regulation and expansion of natural or inducible regulatory T cells, a skewing from a Th2 to a Th1 profile, and the development of anergy and/or deletion in antigen-specific cells [88•]. More rigorous mechanistic studies are required for better understanding of OIT efficacy and outcome. The role of novel adjunct therapies such as omalizumab, probiotics, and possibly anti-IL4 in conjunction with OIT also requires further investigation.

Adverse reactions from OIT may be triggered by different factors, including colds, exercise, alcohol, and NSAIDs. With time, patients may stop OIT for various reasons, including rate of reactions, taste aversion, or difficulty complying with regular doses. In addition, while QoL appears to improve after OIT [89–91], longitudinal studies may help evaluate if this effect is persistent. Currently, patients who are contemplating initiating OIT must carefully consider the possibility of continuing daily ingestion for years, with no current prospect of cure using solely this approach. Hence, in order to evaluate further the clinical applicability and value of OIT, much larger and longer longitudinal studies using the same homogenous protocol are needed to compare long-term QoL, and the safety and efficacy of OIT in desensitized patients, compared to control patients who are practicing dietary elimination.

Conclusion

Most OIT trials have led to successful food desensitization on the short term in the majority of patients; however, there have been tremendous heterogeneity in the approach. Much larger, longer, and more homogenous studies are needed to evaluate the long-term safety and efficacy of OIT and its effect on QoL.

Compliance with Ethical Standards

Conflict of Interest Dr. Rachid declares grants from Aimmune, from Food Allergy Research and Education and from CSL-Behring.

Dr. Yee declares no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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