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Specific Oral Tolerance Induction in Childhood

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Abstract

Food allergy continues to be a significant public health concern for which there are no approved treatments and management strategies primarily include allergen avoidance and pharmacological measures for accidental exposures. Food allergy is thought to result from either a failure to establish oral tolerance or the breakdown of existing oral tolerance,

therefore, experimental preventative and treatment strategies are now aimed at inducing specific oral tolerance. This may occur in infancy prior to the development of food allergy through the optimal timing of dietary exposure (primary oral tolerance induction) or as a treatment for established food allergy through oral immunotherapy (secondary oral tolerance induction). Trials examining the effectiveness of early dietary allergen exposure to prevent food allergy have yielded promising results for peanut allergy but not so for other allergens, although the results of several trials are yet to be published. Although infant feeding guidelines no longer advise to avoid allergenic foods and exposure to food allergens orally is an important step in inducing food tolerance by the immune system, evidence regarding the optimal timing, dose and form of these foods into the infant's diet is lacking. Likewise, oral immunotherapy trials appear promising for inducing desensitisation however the long term efficacy in achieving sustained desensitisation and optimal protocols to achieve this are unknown. More research is needed in this emerging field.

Introduction

Food allergy continues to be a significant public health concern. The prevalence of food allergies has increased in recent decades (1-3) with a recent study suggesting the epidemic is yet to reach its peak as hospitalisations for food-induced anaphylaxis continue to rise. (4) There are no approved treatments for food allergy and management strategies primarily include allergen avoidance and pharmacological measures for symptom control following accidental exposure, including antihistamines for mild reactions and intramuscular adrenaline for those that are severe. Despite vigilant efforts by most, accidental exposures may still occur and families can experience significant anxiety around dietary choices and fear of severe reactions resulting in reduced quality of life. (5)

A proportion of children with food allergy will outgrow the disorder indicating that oral tolerance can develop in previously allergic individuals. This is dependent on the type of allergen the child is allergic to, with studies on the natural history of food allergy demonstrating that tolerance develops more frequently in egg and milk allergic individuals compared to peanut (6-8). Oral tolerance is the active inhibition of immune responses to food proteins previously encountered by the gastrointestinal tract and food allergy is thought to result from either a failure to establish oral tolerance or the breakdown of existing oral tolerance (9, 10). Therefore, experimental preventative and treatment strategies are now

aimed at inducing specific oral tolerance. This may occur in infancy prior to the development of food allergy through the optimal timing of dietary exposure (primary oral tolerance induction) or as a treatment for established food allergy through oral immunotherapy (secondary oral tolerance induction). This article reviews the literature surrounding specific oral tolerance induction in children.

The Development of Food Allergy and Induction of Oral Tolerance

Food allergy is classically associated with an imbalance between Th1/Th2 responses. Individuals who have not acquired tolerance to a specific food during early childhood exhibit a Th2 response which is associated with IL-4 and IL-13 cytokine-dependent inflammation and subsequent B cell production of IgE antibodies. Food allergy is characterised by elevated levels of food-specific IgE antibodies in conjunction with clinical reactivity, as well as increased Th2 cells and low regulatory T cell cytokine responses to the allergen. (11)

Oral tolerance is the active inhibition of cellular and humoral immune responses to food antigens. This inhibition occurs through several mechanisms including the production of regulatory T cells and the deletion of antigen-specific T cells. In studies of the natural history of food allergy the development of tolerance is associated with a decrease in food-specific IgE antibodies and concurrent increase in IgG4 antibodies (12, 13). Tolerant children exhibit a Th1 predominant cytokine responses, low or absent IgE antibodies and do not clinically react to the allergen (10, 14). Allergen specific therapies aim to induce oral tolerance which can be also be measured immunomodulatory responses, such as reduced IgE antibodies and increases in IgG4 and regulatory T cells which suppress the allergic response.

With an increased understanding of oral immune tolerance together with results from epidemiological studies and recent clinical trials, current guidelines concerning the prevention of food allergies through allergen avoidance have been called into question. Burks *et al.* suggested that increased understanding of the mechanisms involved in tolerance has shifted the focus of treatment and prevention towards inducing tolerance, through allergen exposure (15). There is emerging evidence to suggest that exposure to the proper dose of antigen during a critical period in early life is important for the shaping of the appropriate immune response to foods (16).

Primary Oral Tolerance Induction – Prevention of food allergy

Early preventative strategies to curb the rise in food allergies were aimed at allergen avoidance, specifically maternal allergen avoidance during pregnancy and lactation, and the delayed introduction of allergens into the infant's diet. These avoidance policies were based on little scientific evidence and subsequent observational studies have shown that these measures are ineffective. In fact, delayed introduction of allergenic foods into the infant's diet has now been shown to increase the risk of food allergy (through an RCT for peanut allergy and observational studies for egg, wheat and cow's milk) and it is postulated that there is an optimal window of oral allergen exposure to induce immune tolerance (17-20). The "dual-allergen exposure" hypothesis proposes that sensitisation to food allergens occurs through low-dose cutaneous exposure in infants with skin barrier dysfunction, such as eczema. It has been shown that exposure of infant's inflamed skin to peanut protein in topical creams is associated with an increased risk of peanut allergy (21). Food tolerance is subsequently induced by exposure to allergens through the oral route and therefore the development of food allergy depends on the timing and balance between cutaneous and oral exposure (22). Considerable interest now surrounds the hypothesis the early introduction of allergens into the infant's diet will induce oral tolerance and therefore prevent the development of food allergy.

RCTs on the prevention of peanut allergy through early dietary exposure

Table 1 summarises recent randomised controlled trials and those currently in progress investigating whether early introduction of solids can prevent food allergy. The LEAP study is a randomised open-labelled trial which aimed to determine whether the early introduction of dietary peanut, as opposed to peanut avoidance, can prevent peanut allergy. Infants considered to be at high risk of peanut allergy on the basis of having egg allergy, severe eczema or both were recruited between 4-11 months of age. Participants were stratified based on their SPT response to peanut (0mm versus 1-4mm; SPT>4mm excluded) and within the strata were randomised to either consume 6g of peanut protein per week or no consumption until 5 years of age. In SPT negative children, the prevalence of peanut allergy in consumption vs. no consumption group was 1.9% and 13.7% respectively ($p<0.0001$) which represents a risk reduction in peanut allergy of 86%. In SPT 1-4mm children, the prevalence of peanut allergy was also lower in peanut consumption versus no consumption group (10.6%

and 35.3% respectively p=0.004), representing a risk reduction of 70%. Immunological markers also differed between the peanut consumption and no consumption groups at follow-up. Both the mean SPT wheals and number of markedly elevated peanut-specific IgE levels were higher in the avoidance group. In contrast, the peanut consumption group had higher peanut IgG and IgG4 levels, measures that are associated with tolerance (23).

Although this study has received much attention, questions remain as to how these findings can be implemented at the population level. Due to the increasing problem of peanut allergy and few available preventative strategies, the accompanying editorial called for widespread screening of at risk infants. It proposed that infants at risk of peanut allergy should undergo SPT and those who are non-sensitised should include peanut into their diet whilst those with mild sensitisation should undergo a food challenge prior to incorporating peanut into the diet. (24) However applying these recommendations at the population level pose significant barriers. Using the HealthNuts population-based sample of 5276 infants, Koplin et al found that 16% of the population would require screening yet would miss 23% peanut allergy cases at the population level. (25) Several questions remain that the LEAP trial and current research are yet unable to answer. The effectiveness of early peanut introduction in sensitised infants with SPT > 4mm is not known as these infants were presumed to be already peanut allergic and excluded from the LEAP study. SPT as a screening step in those who are at high risk is controversial and there is general consensus that population based SPT screening would be both prohibitively expensive and possibly lead to over-diagnosis of food allergy. Finally, it is not known whether early introduction of peanut is an effective preventative strategy in those who are not considered at high-risk as the LEAP study only included infants with a history of egg allergy or severe eczema.

RCTs on the prevention of egg allergy through early dietary exposure

Two studies have addressed whether early introduction of egg into the infants diet is an effective measure to prevent egg allergy. The STAR trial recruited high-risk infants with moderate-severe eczema at 4 months of age and randomised them to receive either 0.9g of egg protein powder or placebo (rice powder) per day from 4 to 8 months of age. The prevalence of egg allergy at 12-months was lower in the intervention arm compared to the placebo but did not reach statistical significance (33% and 51% respectively, p=0.11). Unexpectedly, a high proportion of infants reacted to the study powder, mostly at the first

exposure. 31% (15/49) of infants in the intervention group reported an allergic reaction to the egg powder, including 1 case of anaphylaxis and 8% (3/37) of the placebo group reacted to the rice powder. As a result, this trial was terminated early which may have resulted in insufficient power to detect a statistically significant effect, although the current results suggest a trend towards allergy prevention. Immunological assessment showed that infants who consumed egg protein had significantly higher IgG4 levels at follow-up, which are markers of tolerance (26).

The results of the HEAP study are only available in abstract form at this point in time. In this study, 184 infants received pasteurised egg white powder 3 times a week compared to 199 infants in the placebo group who received rice powder starting at 4-6 months until 12 months of age. Early consumption of pasteurised egg was not effective in preventing egg allergy. In contrast to the STAR trial, this study was population-based and infants were screened for pre-existing egg allergy. Despite this, three of 184 infants reacted to the egg powder at first exposure including one episode of anaphylaxis (27). Three other studies are currently in progress, STEP and BEAT assessing egg allergy and PreventADALL assessing egg, peanut and milk allergy; the results are eagerly anticipated.

RCTs on the prevention of food allergy through early dietary exposure

The recently published EAT study compared the early introduction of 6 allergenic foods (peanut, egg, cow's milk, sesame, fish and wheat) from 3 months of age to standard introduction of solids from 6 months of age in exclusively breastfed infants, with the primary outcome being reduced food allergy. (28) Unfortunately, the study failed to show a significant reduction in food allergy at 1-3 years of age with food allergy occurring in 7.1% of the standard-introduction group compared 5.6% of the early-introduction group (p=0.32).This may be reflective of poor compliance in the early introduction group (only 42% consumed the target doses of the allergenic foods), or because the age at allergen introduction in the intervention and control groups may not have been different enough to have a biological effect.

Implications

Importantly, the EAT study found that the early introduction of solids at the population level was safe and did not negatively impact breastfeeding rates, a concern held by some community groups. (29) However, an unexpectedly high number of adverse events were reported in the STAR trial, and to a lesser extent HEAP. In the STAR trial a significant number of infants reacted to egg protein on their first known exposure, suggesting that sensitisation to egg had occurred prior to 4-6 months of age, possibly in utero, during breastfeeding or via cutaneous exposure. This may be reflective of population differences, EAT was population-based whereas STAR comprised of high risk infants. Alternatively, the form that the food was administered may play an important role in safety. Regular cooked egg was used in EAT with few adverse events reported however pasteurised egg protein powder which is more allergenic was administered in both STAR and HEAP where more adverse events were seen.

Although infant feeding guidelines no longer advise to avoid allergenic foods in the infant's diet (30) evidence regarding the optimal timing, dose and form of these foods into the infant's diet is lacking. Exposure to food allergens orally is an important step in inducing food tolerance by the immune system and the early introduction of both egg and peanut is associated with immune tolerance induction pathways demonstrated by higher food-specific IgG4 levels in consumption groups compared to avoidance groups in both LEAP and STAR. However it is not clear from current studies what age is optimal for exposure to allergenic solids to prevent allergy, nor the minimum dose required.

Secondary Oral Tolerance Induction – Treatment of food allergy

In established food allergy where the primary induction of oral tolerance has failed, emerging therapies are using similar mechanistic principles of regular, low-dose allergen exposure as a treatment for a food allergy. The primary goal of oral immunotherapy is to induce non-responsiveness of the immune system when re-exposed to the allergen by inducing immunomodulatory responses which suppress the allergic response. This can result in either desensitisation or sustained unresponsiveness. Desensitisation is defined as a change in the threshold dose of an ingested food allergen necessary to cause allergic symptoms, a state dependent on the ongoing antigen exposure. Markers of desensitisation include increased

IgG4 and reduced IgE as well as decreased activation and release of inflammatory mediators by mast cells and basophils (23, 31). By contrast, sustained unresponsiveness is the induction of long-term immunological changes associated with the ability to ingest a food without symptoms and without ongoing therapy and has recently been proposed in preference to tolerance when describing immunotherapy outcomes (32). The mechanisms of this tolerance induction include the active modulation of the immune response to promote regulatory T cell development and immunological skewing away from a Th2 response (11, 31, 33), with the addition of regulatory B cells recently found to significantly affect immune tolerance in food allergies (34, 35).

Oral immunotherapy trials

Tables 2-4 summarise characteristics of OIT trials for peanut (12), egg (5) and milk (10). Collectively the data shows that OIT trials vary in study design, protocols and outcomes. The majority of studies were small with less than 50 participants; 4 peanut, 3 egg and 1 milk studies had 20 or fewer participants (36-43). OIT protocols varied in terms of the build-up and maintenance time period, maintenance dose and amount of food required to be tolerated at follow-up OFC to declare desensitisation and tolerance. Standardisation of OIT protocols is lacking and we are yet to discover the optimal induction and maintenance scheduling and whether they differ by patient age or underlying severity of disease. (44)

Outcomes of OIT studies: Desensitisation versus sustained unresponsiveness

All studies reported high rates of desensitisation, defined as the ability to pass a food challenge at conclusion of the OIT protocol. Desensitisation following peanut OIT ranged from 62% to 100%, egg OIT 57% to 94% and milk OIT 36% to 90%. However, the long-term implications of this are largely unknown because few studies evaluated sustained unresponsiveness which is the continued tolerance following a period of allergen avoidance after successful desensitisation. For peanut OIT sustained unresponsiveness was achieved in 14% to 50% participants following avoidance for 2 weeks to 3 months (38, 45-47) and was as high as 82% in a recent study that used an adjuvant probiotic to achieve sustained unresponsiveness after 2-5 weeks avoidance (48). For egg OIT, sustained unresponsiveness was achieved in around 30% of participants following up to 3 months of continued avoidance (40, 49, 50). In other words, after discontinuing the therapy, egg allergy recurred in 70% of

children following 3 months of egg avoidance (50). Similar results are reported for milk (51). At this stage it is unclear whether the therapy needs to be continued lifelong to maintain tolerance.

Adverse events

Adverse reactions during OIT are common and have contributed to participant drop-out in some studies. Adverse reactions among those who continue with OIT are often mild and usually managed with antihistamines, however severe reactions also occur. In one milk OIT, 47% of participants reported moderate adverse reactions (52) whilst in another large milk OIT, 46% of participants (n=280) required epinephrine during the induction phase and 15% of participants required epinephrine use at home. (53) Adverse events during egg OIT have occurred in as many as 70% of participants (n=14/20) with most requiring pre-medications. (41) In a study of 50 children examining the safety of egg OIT, 26% of children required adrenaline. Predictors of more frequent and severe reactions to egg OIT were underlying asthma, high egg-sIgE and lower threshold dose on baseline DBPCFC. (54) Adverse reactions are a significant barrier for bringing OIT to clinical practice.

Adverse reactions during OIT may also have unintended consequences. Before the development of OIT protocols, patients were advised that allergen avoidance was the only treatment for food allergy and even mild symptoms from accidental ingestions were to be feared and avoided to minimize the risk of a more severe allergic reactions. By contrast, most OIT protocols report a high rate of adverse events including allergic reactions involving the respiratory system requiring epinephrine. There is concern that by advising patients to continue OIT despite the development of allergic symptoms involving the airway, could send the wrong message that allergic reactions to food are acceptable. As such, an unexpected adverse side-effect of OIT protocols might be the desensitisation of patients and families to signs of allergic reactions rather than the development of tolerance to the food itself. With the paradigm shift in thinking about allergen avoidance as unnecessary for allergy prevention, it must be ensured that allergen avoidance remains central to the care of those with confirmed food allergy and who are at risk of anaphylaxis (44).

Limitations of current OIT trials

Only a few studies compared OIT to a placebo (46, 48-50, 55-57). It is well known that food allergy is transient in some individuals with an estimated 20% of children allergic to peanut and 80% allergic to egg and milk expected to naturally develop tolerance (6, 8, 58-60). Therefore, without an adequate control arm, it is difficult to ascertain whether the treatment effect was entirely due to OIT itself, or what would have occurred incidentally considering the natural history of food allergy. In studies with a comparison group, either placebo or allergen avoidance, it is evident that OIT is superior to the control, although desensitisation occurs in up to 15% of participants in the control arms in some studies (48, 50, 57).

In one study (not included in the summary tables because results were presented for egg and milk OIT combined) development of tolerance in the control arm was the same as the OIT arm (36% and 35% respectively) (61). In addition, current OIT studies are generally not controlled for factors that are known to predict the development of tolerance. For example, egg allergic infants who are able to tolerate baked egg are more likely to develop tolerance and this underlying phenotype may interact with the effectiveness of OIT (7). Samples also varied in age, a factor that is also know to influence the natural history of food allergy. (58) Only one OIT study accounted for factors that are associated with the natural development of tolerance and randomised participants based on age (> and < 5 years) and SPT wheal size (> or < 10mm) (48).

Mechanism and biomarkers

Food allergy is the consequence of either a failure to establish oral tolerance or an interruption of existing tolerance, resulting in dysregulated Th2 responses and immediate hypersensitivity reactions upon antigen re-exposure. A decrease in the Th2 phenotype is important for the success of OIT, with patients who have successfully undergone peanut OIT (45) and egg OIT (41) from two separate studies showing that shift away from Th2 cytokine production by peripheral blood mononuclear cells. More recent evidence supports that impairment in regulatory T cell induction and innate immunity might contribute to Th2 polarization in food allergic patients. Syed *et al*. highlighted the importance for the induction of allergen-specific Tregs, which correlated with clinical reactivity in a phase 1 study (46) of 23 participants undergoing peanut OIT over a 24-month period. In patients who regained

sensitivity to peanuts, the FOXP3 gene in antigen induced regulatory T cells became methylated compared patients who remained tolerant after 6 months post immunotherapy staying de-methylated, suggesting cellular changes in immune responses may precede humoral immune modulation.

However, there is a clear lack of biomarkers or standardized guidelines for assessing the likely long-term effectiveness of OIT in inducing tolerance. Desensitization is seen to be associated with changes in a number of immunological parameters, indicative of immune modulation. In patients who have undergone egg OIT, patients who were able to tolerate significantly higher doses of egg protein than noted at entry had decreased skin test size, reduced egg specific IgE levels, and increased IgG4 levels. (40, 62) More recently, findings from milk and peanut OIT trials have found that there is no significant difference in the IgE levels after immunotherapy. However both milk and peanut specific IgG4 levels significantly increased. (23, 46, 63, 64) A meta-analyses of 21 trials indicates that desensitization is associated with a significant reduction in skin prick test responses to the relevant food (mean difference —2.96 mm, 95% CI 4.4–1.45) and an increase in specific IgG4 levels (average increase 19.9 µg/ml, 95% CI 17.1–22.6). The majority of studies, however, do not report a reduction in allergen-specific IgE (65). These findings suggest that IgE may not be a useful marker of resolution and is more closely linked to persistent allergy. The challenge remains to identify those that best predict long-term effectiveness.

Future directions

Although clinical desensitization and immune modulation have been demonstrated, the strength of the current evidence from early clinical trial designs is insufficient to change practice. There remains many unanswered questions with regards to OIT. We are yet to discover the optimal induction and maintenance scheduling and whether these differ by patient age, underlying severity of disease or levels of immunological biomarkers. It is not known whether these early positive findings will be replicated when tested in trials with larger numbers of participants. Little is known about post-immunotherapy outcomes and whether OIT needs to be long-term or even indefinite or what the likelihood of allergic relapse is following cessation of treatment. These issues will be difficult to tease out because

recruitment of food allergic patients into double-blind study protocols can be difficult. This is due to the risk of anaphylaxis to these patients both from challenges required to validate entry criteria as well as outcome measures but also from the therapy itself (44).

Although the rapid growth in publications outlining partial success from various OIT protocols offers an exciting development and real hope for patients, substantially more data on long-term safety and effectiveness are required before widespread adoption in clinic is likely. In addition, a note of extreme caution needs to be sounded because of the risks inherent to study participants. This includes both anaphylaxis and the risk that patients themselves might attempt initiation of OIT protocols at home without appropriate medical supervision. Of further concern is the wide variation in protocol methodologies as well as the lack of standardization of outcome measures. The persistent heterogeneity of study design and quality will ultimately curtail the ability to formally assess the overall effectiveness of OIT protocols across multiple centres, a regulatory requirement before such therapies could be safely considered for routine clinical use (44).

Conclusion

Current therapeutic strategies are focused on harnessing oral tolerance to modulate the allergic response using antigen specific modalities. The realization that antigen exposure may drive tolerance is being explored in prophylactic and therapeutic trials for food allergy. It is too early to say whether food allergy can be prevented early in life through early dietary exposure, although early studies for peanut allergy prevention are promising. Whilst OIT for the treatment of food allergy continues to prove more effective than avoidance diets, evidence points more to a phenomenon of transient desensitization rather than long-term tolerance. It is possible that many years of OIT may be required to induce long-term tolerance in patients with food allergy. More data on long-term safety and effectiveness is required before widespread adoption in clinic.

Table 1. Randomised controlled trials investigation the intervention of early introduction of allergens for food allergy prevention

Trial	Allergen	Sample size	Population	Intervention	Outcome	Results
LEAP (Learning Early About Peanut allergy) Du Toit 2015 (23)	Peanut	628	Infants aged 4-11 months with severe eczema and/or egg allergy.	Participants stratified by SPT, 0mm wheal (n=530) and 1-4mm wheal (n=98) (SPT>4mm excluded). Infants randomly assigned to no peanut consumption or consumption of 6g of peanut protein per week until 5 years of age.	Peanut allergy at age 5 years (OFC)	SPT 0mm: prevalence of peanut allergy in consumption vs. no consumption group was 1.9% and 13.7% respectively (p<0.0001) SPT 1-4mm: prevalence of peanut allergy in consumption vs. no consumption group was 10.6% and 35.3% respectively (p=0.004)
EAT (Enquiring about Tolerance study) Perkin 2016 (28)	Peanut, egg, cow's milk, sesame, fish, wheat	1162	Population-based. Exclusively breast-fed 3 month old infants	Infants randomised to standard introduction (exclusive breastfeeding until 6 months of age followed by solids introduction at the parents discretion n=595) or early introduction (2g of each allergen protein twice weekly n=567)	Food allergy between 1 and 3 years of age (OFC).	Prevalence of food allergy was 7.1% of those in the standard-introduction group and 5.6% of the early-introduction group (p=0.32).
HEAP (Hen's Egg Allergy Prevention) Bachell 2015 (27)	Egg	406	Population-based	Pasteurized egg white powder (n=184) versus placebo (n=199) 3 times a week starting at age 4-6 months until age 12 months under a concurrent egg-free diet.	Egg allergy at age 12-months. (sIgE and OFC)	Intervention: egg allergy n=2 Control: egg allergy n=1 (Results in abstract form)
STAR (Solids Timing for Allergy Research) Palmer 2013 (26)	Egg	86	Infants age <4 months with moderate-severe eczema	0.9g pasteurized raw whole egg powder per day (n=49) versus placebo (n=37) from age 4-8 months	Egg allergy at 12-months (SPT and OFC)	Prevalence of egg allergy was 33% in intervention group and 51% in control group. (RR 0.65, 95% CI, 0.38-1.11 p=0.11)
BEAT (Beating egg allergy trial) (66)	Egg	332	Infants age < 4 months with atopic first	0.5g egg protein powder per day from 4-6months	Egg sensitisation (SPT) and	Recruitment complete; results not published yet.

			degree relative	until 12 months versus placebo	allergy	
STEP (Starting time for egg protein)(67)	Egg	820	Infants age 4-7 months with maternal history of atopy.	1/3 teaspoon whole egg powder per day from 4-6.5 months until 10 months versus placebo	Egg allergy (SPT and OFC) at 12 months	Recruitment complete; results not published yet.
PreventADALL (68)	Egg, milk, wheat and peanut	2500	Population-based birth cohort.	Systematic introduction of egg, milk, wheat and peanut by 4 months of age and/or skin care versus placebo	Food allergy and atopic dermatitis	Recruitment in progress

OFC: oral food challenge; SPT: skin prick test;

Table 2: Peanut OIT studies

Author	Design	Sample size[1]	Age (years)	Allergy at baseline	Maintenance Dose	Duration	Peanut tolerated in follow-up OFC	Outcome
Tang 2015 (48)	DBPCT with adjuvant probiotic	56 (OIT n=28)	1-10	Clinical history and SPT/sIgE	2g	18 months	4g	SU after 2-5 weeks avoidance: OIT 82.1%, placebo 3.6%. Desensitisation: OIT 89.7%, placebo 7.1%
Narisety 2015 (38)	DBPCT (OIT/SLIT placebo vs. SLIT/OIT placebo)	16	7-13	Clinical history and SPT/sIgE plus OFC to 1g peanut protein	2g	12-18 months	10g	SU after 4 weeks avoidance: 25%
Bird 2015 (36)	Open label	9	4-16	DBPCFC	2g	4 months	5g	Desensitisation: 100%
Vickery 2014 (47)	Open label	24	1-16	Clinical history and SPT/sIgE	Up to 4g	Up to 5 years	5g	SU after 4wk avoidance: 50%
Anagnostou 2014 (55)	Randomised crossover trial	39	7-16	DBPCFC	800mg	6 months	1.4g	Desensitisation: OIT 62%, placebo 0%
Syed 2014 (46)	Open label OIT compared to avoidance	43 (OIT n=23)	4-55	DBPCFC	4g	Up to 2 years	4g	SU after 3 months avoidance:57% Desensitisation: OIT 87%, control 0%
Schneider	Open label	13	8-16	DBPCFC	4g	32	8g	Desensitisation:

2013 (39)	OIT with omalizumab					weeks		92%
Varshney 2011 (56)	DBPCT	25 (OIT n=16)	2-10	Clinical history and SPT/sIgE	4g	48 weeks	5g	Desensitisation: OIT 100%, placebo 0%.
Anagnostou 2011 (69)	Open label	22	4-18	OFC	800mg	Up to 68 weeks	6.6g	Desensitisation 64%
Blumchen 2010 (45)	Open label	23	3-14	DBPCFC	500mg	Up to 22 months	4g	64% reached maintenance of 500mg peanut (14/22). SU after 2 weeks avoidance: 14% (3/22)
Jones 2009 (70)	Open label	29	1-10	Clinical history and SPT/sIgE	1.8g	Up to 36 months	3.9g	Desensitisation: 93%
Clark 2009 (37)	Open label	4	9-13	DBPCFC	800mg	10 weeks	2.4g	Desensitisation 75%

DBPCT: Double-blind, placebo-controlled randomized trial; DBPCFC: double-blind placebo-controlled food challenge; OFC: oral food challenge; OIT: oral immunotherapy; SLIT: sublingual immunotherapy; SU: Sustained unresponsiveness

1. Number that completed study protocol (excludes dropouts)

Table 3: Egg OIT studies

Author	Design	Sample size	Age (years)	Allergy at baseline	Maintenance Dose	Duration (months)	Egg tolerated in follow-up OFC	Outcome
Perezábad 2015 (41)	Open label	20	5-15	Clinical history and SPT/sIgE and OFC	32mL of pasteurized EW and graded dietary exposure	Up to 24	32 mL of pasteurized EW	Desensitisation 60%
Caminiti 2015 (50)	DBPCT	31 (OIT=17)	4-11	DBPCFC	4g dehydrated EW	4 months OIT, followed by 6 months dietary exposures then 3 months avoidance	3.7g egg white plus 1 fresh egg on day 2	Desensitisation: OIT 94%, placebo 0% SU after 6 months ingestion then 3 months avoidance: OIT 31% , placebo 7%
Burks 2012 (49)	DBPCT	55 (OIT=40)	5-11	Clinical history and SPT/sIgE	2g EW powder	22	10g EW powder plus 1 whole cooked egg	Desensitisation: OIT 75%, placebo 0% SU after 4-6wk avoidance 28% (maintained for further 12 months with

								continued dietary egg exposure), placebo 0%
Vickery 2010 (42)	Open label	8	3-13	Clinical history and SPT/sIgE	0.3-3.6g	18-50	10g egg	SU 1 month after ceasing OIT 75%
Buchanan 2007 (40)	Open label	7	1-7	Clinical history or sIgE	0.3g	24	10g powdered EW and 1 scrambled egg	Desensitisation 57% SU after 3 months avoidance: 29%

DBPCT: Double-blind, placebo-controlled randomized trial; DBPCFC: double-blind placebo-controlled food challenge; EW: egg white; OIT: oral immunotherapy; SU: Sustained unresponsiveness

Table 4: Milk OIT studies

Author	Design	Sample size	Age (years)	Allergy at baseline	Maintenance Dose	Duration (months)	Amount milk tolerated in follow-up OFC	Outcome
Wood 2016 (71)	Omalizumab DBPCT, open-label OIT	57	7-32	DBPCFC	3.3g	24	10g	Desensitistaion: Omalizumab+OIT 89% OIT only 71% SU after 8 weeks Omalizumab+OIT 48% OIT only 36%
Yanagida 2015 (57)	Open label OIT compared to avoidance	37 (OIT=12)	> 5	OFC	3mL every 5 days	12	3mL and 25mL	Desensitisation to 3 ml OIT 58.3%, avoidance 13.8% Desensitisation to 25 ml OIT 33.3%, avoidance 0%
Levy 2014 (53)	Open label	280	> 4	Clinical history, SPT/sIgE or OFC	Up to 240mL cow's milk (7.2g CMP)	Up to 27	No OFC but tolerated 7.2g CMP in OIT protocol	Desensitisation: 60%
Salmivesi 2012 (72)	DBPCT	28 (OIT=18)	6-14	OFC	6.4g CMP / 200mL/day	6 months DBPC-OIT	200mL. No OFC, phone	Desensitisation: 89%. Maintained for 3 years

						followed by 6 months open OIT for both groups	follow-up	following daily consumption: 79%
Keet 2012 (73)	Open label RCT SLIT vs SLIT and OIT	30 (OIT=20)	6-17	DBPCFC	1-2g	15	8g CMP	Desensitisation: 70% SU after 6wk avoidance 40%
Martorell 2011 (52)	Open label (randomised, OIT vs. avoidance)	60 (OIT=30)	2-3	DBPCFC	200 mL	12	200 mL	Desensitisation: OIT 90%, avoidance group 23%
Pajno 2010 (74)	Randomised, placebo-controlled	30	4-10	DBPCFC	200 mL	4.5	200 mL	Desensitisation: OIT 67%, placebo 0%
Skripak 2008 (43)	DBPCRT	20 (OIT=13)	6-17	DBPCFC	500mg	23 weeks	8g CMP	Median OFC threshold dose increased from 40 to 56140 mg
Longo 2008 (75)	Open label, randomised OIT vs. avoidance	60 (OIT=30)	5-17	DBPCFC	150ml	1 year	OIT group tolerated 150ml dose (no OFC) Placebo: DBPCFC	Desensitisation: OIT 36%, placebo 0%
Meglio 2004 (76)	Open label	21	6-10 years	Clinical history or DBPCFC	200ml	6 months	200mL OIT dose (no OFC)	Desensitisation: 72%

CMP: cow's milk protein; DBPCT: Double-blind, placebo-controlled randomized trial; DBPCFC: double-blind placebo-controlled food challenge; OFC: oral food challenge; OIT: oral immunotherapy; SU: Sustained unresponsiveness

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