



Randomized controlled trials investigating the role of allergen exposure in food allergy: where are we now?

Jessica Metcalfe, Susan L. Prescott, and Debra J. Palmer

Purpose of review

The dramatic increase in food allergy stresses the need for more definitive treatment strategies that induce lasting oral tolerance in tandem with more effective approaches to primary prevention. Allergen-induced oral tolerance is now of prime interest in both of these settings as a potentially more effective approach to traditional avoidance strategies. Here, we review the recent randomized controlled trials (RCTs) examining the controlled allergen exposure in both treatment and prevention of food allergy.

Recent findings

Collectively, RCTs of oral immunotherapy (OIT) for the treatment of food allergy increase the amount of food allergen that can be tolerated. Allergic side-effects are common and this remains a major obstacle to general use in clinical practice. There are also at least eight RCTs currently in progress investigating early allergen exposure for the primary prevention of food allergy.

Summary

OIT is showing promise as a possible treatment for food allergy; however, more large, longitudinal studies are needed to optimize both safety and efficacy and to assess the long-term effects, before this can be considered in clinical practice. The results of the primary prevention studies will be of great importance in determining the role of earlier introduction of allergenic foods in reducing the burden of food allergy.

Keywords

allergen exposure, food allergy, oral immunotherapy, oral tolerance, randomized controlled trial

INTRODUCTION

The incidence of food allergy has increased dramatically over the last 10–20 years, with the greatest burden of this new epidemic affecting young children particularly in their first years of life. In developed regions such as Australia, recent studies have found more than 20% of 1-year-olds are now sensitized to foods and that more than 10% have clinical challenge-proven, IgE-mediated food allergy [1]. Food anaphylaxis in preschool children has also substantially increased, with a five-fold rise in over just 10 years [2]. Similar trends are now emerging in the developing regions [3]. Along with increasing persistence of disease [4], this is contributing to a growing burden of food allergy in many communities.

Traditionally, the only treatment available for a food allergy has been a strict avoidance diet of the food allergen. These diets are difficult to maintain, and accidental exposure is still likely, with many individuals on avoidance diets still experiencing

severe reactions [5]. The ever-present fear of potentially life-threatening reactions places the families under enormous stress, and has been shown to substantially decrease the quality of life when compared with the general population, and to an even greater extent than seen in other chronic conditions [6].

There has been recent debate around whether allergen ‘controlled exposure’ rather than ‘complete avoidance’ may be the ultimate solution for both treatment and prevention of food allergy. The merits of various allergen-based delivery

School of Paediatrics and Child Health Research, University of Western Australia, Perth, Western Australia, Australia

Correspondence to Debra J. Palmer, PhD, School of Paediatrics and Child Health Research, University of Western Australia, PO Box D184, Princess Margaret Hospital, Perth, WA 6001, Australia. Tel: +61 8 9340 8171; fax: +61 8 9388 2097; e-mail: debbie.palmer@uwa.edu.au

Curr Opin Allergy Clin Immunol 2013, 13:296–305

DOI:10.1097/ACI.0b013e3283609671

KEY POINTS

- Controlled food allergen exposure may be a more favourable approach than food allergen avoidance in both primary prevention and treatment of food allergy.
- Oral immunotherapy trials are providing evidence that oral desensitization is possible in some food allergic individuals; however, concerns about safety and sustained effectiveness need to be addressed before translation into routine clinical practice can occur.
- Results from the ongoing trials using early regular food allergen exposure for the primary prevention of food allergy are eagerly awaited.

strategies are currently being investigated in an attempt to reduce the burden of food allergy, including subcutaneous injections, sublingual therapy and oral immunotherapy (OIT), which has also been referred to as specific oral tolerance induction (SOTI) and oral desensitization. Although the doses and intervals vary widely between the studies and delivery methods [7], each of these strategies generally involves the regular administration or ingestion of small 'doses' of a particular food allergen with gradual up-scaling to achieve 'maintenance' doses aimed at inducing lasting immune tolerance. The role of regular early introduction of allergenic foods (such as egg and peanut) during infancy is also currently being investigated for the primary prevention of food allergy in a number of randomized controlled trials (RCTs). This review will largely focus on the RCTs published (or in progress) over the last 5 years (2007–2012) using OIT for either the treatment or the prevention of food allergy. Trials on subcutaneous injections or sublingual therapy approaches are beyond the scope of these discussions.

ORAL IMMUNOTHERAPY PROTOCOLS FOR THE TREATMENT OF FOOD ALLERGY

The notion of using immunotherapy for the treatment of food allergy is not new; however, high rates of serious adverse events during early attempts with subcutaneous food immunotherapy deterred further studies and this method was deemed unsuitable for routine clinical practice [8,9]. Alternatively, orally administered food allergens in gradually increasing doses have demonstrated more promise as a treatment method in both case studies [10,11] and uncontrolled trials [12,13]. Although there are now multiple trials investigating the efficacy and safety of OIT for the treatment of food allergy, many are still uncontrolled [14–18].

One of the first published controlled trials of OIT by Patriarca *et al.* [19] demonstrated that oral desensitization to a wide variety of food allergens (including cow's milk, egg and fish) was effective in 83% of participants in the treatment group, compared with none of the participants on a food allergen elimination diet. These favourable findings in a controlled study design gave greater credence to OIT as a definitive therapy in some patients, prompting many other investigators to refine protocols and further study this concept, focusing on the most common food allergens such as hen's egg, cow's milk and peanut. Traditionally, control groups consisted of individuals randomized to maintain an 'allergen-free' diet as in the study by Patriarca *et al.* and it is only recently that placebo products have been introduced to enable the use of gold-standard, double-blinded randomized controlled study design. The use of a double-blinded RCT design improves the available quality of evidence for the efficacy and safety of OIT for food allergy treatment.

Since 2007, there have been eight published RCTs [20²², 23–27] examining the effect of OIT on cow's milk (six of eight), hen's egg (three of eight) and peanut (one of eight) allergic children. The different protocols and designs of each of these [20²², 23–27] are shown in Table 1. One of the distinct differences in the design of these studies is that four used an unblinded RCT protocol in which the control group maintained an allergen-free diet [22²⁵, 25–27], whereas the other four trials used a blinded, placebo-controlled study design [20²¹, 23, 24]. Dosing schedules, treatment periods and measures of efficacy varied across trials, making the direct comparison difficult. However, they all generally followed the same basic three-phase treatment. This involves an initial gradual oral introduction of a food allergen, followed by dose escalations over time to reach a maintenance dose, which is then consumed regularly. Protocols range from 4 to 24 months in the treatment duration and all performed an oral food challenge (OFC) at completion to measure the efficacy of the treatment.

OUTCOMES AND CLINICAL EFFICACY OF ORAL IMMUNOTHERAPY FOR THE TREATMENT OF FOOD ALLERGY

A variety of methods have been used to evaluate the efficacy of OIT in these trials (Table 1); however, all include a clinical measure, usually a double-blinded, placebo-controlled food challenge (DBPCFC) in combination with skin prick testing (SPT) and immunological markers such as immunoglobulin E (IgE) and immunoglobulin G4 (IgG4)

Table 1. Recent randomized controlled trials on food allergen exposure for the treatment of food allergy

Study	Inclusion criteria	Oral immunotherapy (OIT) protocol	Food challenges and efficacy measures	Withdrawals	Main results	Safety
Burks <i>et al.</i> 2012 [20 [■]] USA Hen's egg Double-blind placebo controlled (n=55)	Egg allergic children 5–18 Years old without a history of anaphylaxis Defined as: 1. Six years and older specific IgE greater than 5 kU/l 2. Between 5 and 6 years old specific IgE greater than 12 kU/l No DBPCFC at baseline	Intervention group (n=40): Maintenance phase: 2 g of egg white powder daily Treatment duration 22 months Control group (n=15): Placebo for 10 months only	Oral food challenge (OFC) at 1. 10 months of OIT: 5 g of egg white powder (both groups) 2. 22 months of OIT: 10 g of egg white powder (intervention group only) 3. 24 months after 4–6 weeks egg-free period: 10 g egg white powder and one whole-cooked egg SPT at baseline and 22 months egg-specific IgE and IgG4 measured at all time points	Total: 7 Five in active group because of allergic reactions and Two in placebo group: one because of reaction and one because of transport issues	Challenge outcomes: Pass or fail determination 10 months: 22 of 40 (55%) of intervention group passed OFC and 0 of 15 in the control group 22 months: 30 of 40 (75%) passed OFC 24 months 11 of 40 (27%) passed OFC (after egg-free period) Immune outcomes: IgG4: Median IgG4 of tolerant patients at 10, 22 and 24 months was significantly higher than children who reacted SPT: Decreased SPT wheal size from baseline at 22 months was associated with sustained desensitization at 24 months ($P=0.01$)	Doses of epinephrine: 0 No serious adverse events Adverse events were highest in the first 10 months and mostly associated with OIT dosing
Varshney <i>et al.</i> 2011 [21 [■]] USA Peanut Double-blind placebo controlled (n=28)	Peanut allergic children 1–16 years of age Defined as: Reaction within 6 min of peanut ingestion and a peanut-specific IgE >15 kU/l SPT to peanut >3 mm No DBPCFC at baseline	Intervention group OIT (n=19): Peanut flour Control group (n=9): Placebo powder Maintenance phase: 4000 mg protein for 44 weeks Treatment duration: 48 weeks	DBPCFC at 48 weeks. Cumulative intake of 5000 mg peanut protein Peanut-specific total IgE, IgG and IgG4 measured at 2, 6, 9 and 12 months (OFC) Th2 cytokines IL-5 and IL-13 measured from PBMC's cultured with crude peanut extract	Total: 3 All in peanut OIT group early in study because of allergic side-effects	Challenge outcomes: All peanut OIT reaching OFC (16 of 19) consumed entire dose = 5000 mg protein compared with control group = 280 mg protein Immune outcomes: Titrated SPT decreased from baseline in the peanut OIT group ($P<0.001$) Peanut IgG4 levels: increased significantly ($P<0.001$) in peanut OIT group from baseline through 12 months Decrease in IL-5 and IL-13 cytokine levels from baseline in peanut group	Doses of epinephrine: 2 Both in the active OIT group during the initial day escalation phase No epinephrine required during the home doses in the peanut OIT group
Martorell <i>et al.</i> 2011 [22 [■]] Spain Cow's milk (CM) Open, controlled (n=60)	CM allergic children 24–36 months old Defined as: SPT >3 mm and specific IgE level >0.35 kU/l for milk and CM proteins Clinically reactive during DBPCFC at baseline	Intervention group (n=30): Maintenance phase: 200 ml CM daily plus inclusion of dairy in the diet Control group (n=30): CM-free diet Treatment duration: 12 months	DBPCFC after 12 months with 200 ml pure cow's milk Only infants in OIT group not tolerating full dose at home and all of control group challenged CM-specific IgE, IgG and IgG4 measured at baseline and 12 months	Total: 2 1 because of moving house 1 because of poor tolerance of desensitization protocol	Challenge outcomes: 27 of 30 (90%) patients in active group made it to full dose of 200 ml CM daily by 12 months 3 of 23 (13%) in control group passed OFC at 12 months Immune outcomes: Significant decrease in CM-specific IgE levels from baseline to 12 months in active group ($P=0.0001$) Lower specific IgE levels in OIT group ($P=0.006$)	Doses of epinephrine: 2 80% of children in OIT group had clinically significant reactions

Pajno <i>et al.</i> 2010 [23] Italy Cow's milk Single-blind, placebo controlled ($n=30$)	Milk allergic children 5–10 years old Defined as: IgE levels not specified, but had to be present SPT >3 mm for CM DBPCFC positive at baseline	Intervention group: Cow's milk ($n=15$) Control group: Soy milk ($n=15$) OIT = 'weekly updosing' dose doubled every week in clinic for 18 weeks Maintenance phase: 200 ml daily Treatment duration: 18 weeks	DBPCFC after 18 weeks of OIT Cumulative dose of 200 ml of pure CM CM-specific IgE and IgG4 levels measured at baseline, 13 weeks and at OFC after 18 weeks	Total: 3 2 withdrawals in the active group 1 withdrawal in the placebo group	Challenge outcomes: 10 of 15 (77%) achieved total tolerance of 200 ml No change in threshold for the placebo group Immune outcomes: No significant change in IgE levels in either groups from baseline to the end of OIT. Three children with serious adverse events had elevated IgE levels Significant increase in IgG4 levels from 4.52(3.4) to 23.8 (5.3) $\mu\text{g}/\text{ml}$ in the active group ($P=0.003$), but not in the control group	Doses of epinephrine: 2 3 of 15 had severe adverse events requiring termination of OIT
Skripak <i>et al.</i> 2008 [24] USA Cow's milk Double-blind, placebo controlled ($n=20$)	CM allergic children 6–17 Years old and no history of anaphylaxis Defined as: SPT >histamine Milk-specific IgE >0.35 kU/l Positive DBPCFC to 2.5 g or less of milk protein	Intervention group ($n=13$): Nonfat powdered milk Control group ($n=7$): Placebo powder Maintenance phase: 500 mg milk protein for 13 weeks Treatment duration: 23 weeks	OFC at 23 weeks of OIT to cumulative 8 g CM protein. CM-specific α -lactalbumin, β -lactoglobulin and casein SgE, IgG and IgG4 measured at baseline, when maintenance dose reached (week 10) and after 13 weeks of the maintenance dose (week 23)	Total: 1 1 because of persistent eczema during dose escalation phase	Challenge outcomes: (median threshold quantity) Significant increase in the median threshold dose of CM in the OIT group from baseline: 40–5100 mg ($P=0.002$) by the end of treatment No change in the control group: 40 mg Immune outcomes: Increase in IgG4 levels from baseline in the OIT group ($P=0.002$) No change in IgE levels in either groups	Doses of epinephrine: 4 (all in OIT group: 2 during initial in-hospital build-up doses and 2 at home)
Longo <i>et al.</i> 2008 [25] Italy Cow's milk Open, controlled ($n=60$)	Severely CM allergic children Age 5–17 years with IgE levels >85 kU/l and 1 severe allergic reaction DBPCFC positive reactions to small amounts of milk selected for randomisation ($n=60$)	Intervention group ($n=30$): Maintenance phase: 150 ml of CM + all other forms of dairy foods Control group ($n=30$): CM-free diet for 1 year followed by DBPCFC Treatment duration: 12 months	OIT group open feeding of 150 ml of cow's milk at 1 year Elimination group underwent second DBPCFC at 1 year IgE levels and SPT to whole milk measured at enrolment 6 months and 1 year in all individuals	No data available on withdrawals	OIT intervention group: 11 of 30 (36%) of OIT group could ingest 150 ml of CM with no adverse reaction 16 of 30 (54%) had achieved partial tolerance ranging from 5 to 150 ml 3 of 30 (10%) could not continue because of allergic reactions: failed treatment Placebo group: 0 of 30 achieved an increase in oral tolerance Difference between the two groups significantly different ($P<0.001$) CM-specific SgE levels decreased significantly in 15 of 30 within the OIT group	Doses of epinephrine: 5 All doses in OIT group, with 4 during in hospital dosing and 1 given during home dosing (in ED) 1 more child attended ED for a reaction whilst on home dosing

(Continued)

Table 1 (Continued)

Study	Inclusion criteria	Oral immunotherapy (OIT) protocol	Food challenges and efficacy measures	Withdrawals	Main results	Safety
Staden <i>et al.</i> 2007 [26] Germany Hen's egg and cow's milk Open, controlled	Hen's egg allergic or CM allergic ($n=47$) (median age 2.5 years) Defined as: Confirmed positive DBPCFC at baseline No specific IgE or SPT inclusion criteria	Intervention group: Egg OIT ($n=14$) pasteurized cow's milk ($n=11$) Maintenance phase: 3300 mg CM protein or 1600 mg egg protein Control group: Strict avoidance diet ($n=20$, 10 in cow's milk and 10 in hen's egg) Treatment duration: 11–59 months	DBPCFC 18–24 months after enrolment for both groups depending on when induction phase and maintenance were achieved OIT intervention group went on strict elimination diet 2 months before final food challenge	Total: 2 1 in the control group lost to follow-up and 1 in the OIT group which withdrew prior to SPT ($n=45$ who completed the study)	OIT intervention group: Challenge outcomes: 16 of 25 (64%) children able to integrate the allergen into the diet 9 of 25 = permanent tolerance 7 of 25 = partial tolerance Control group: Challenge outcomes: 7 of 20 (35%) children were tolerant ($P=0.05$) sIgE significantly reduced in tolerant children from baseline (from both groups) No change in nonresponders or others in control group	Doses of epinephrine: 0 All OIT children had some form of reaction Control group: 5 Children had mild-to-moderate reactions because of accidental ingestion
Morisset <i>et al.</i> 2007 [27] France Hen's egg (HE) and cow's milk Open, controlled ($n=60$ CM and $n=90$ HE)	CM allergic children aged 13 months to 6.5 years Hen's egg allergic children aged 1–8 years Allergy defined as positive SPT, the presence of specific IgE antibodies and a positive OFC at baseline	CM intervention group ($n=27$): Maintenance phase: 250 ml/day CM, and all dairy products, then unlimited Egg intervention group ($n=49$): Maintenance phase: hard-boiled egg daily and then unlimited egg products CM and egg control group ($n=30$ and 35): strict elimination diet for 6 months Treatment duration: 6 months	SBPCFC performed after 6 months of treatment with 200 ml CM SPT and specific IgE measured at baseline and 6 months	Total: 9 Cow's milk group: 3 Children lost to follow-up 1 of these in the OIT group HE group: 6 Children lost to follow-up 2 of these in the OIT group	CM results: 60% Children in the control group passed the challenge after 6 months versus 88.9% of children in the OIT group SPT decreased significantly in the OIT group after treatment ($P<0.002$) IgE results decreased in both groups Egg results: 51.4% Children in the control group passed the OFC versus 69.4% children in the OIT group Mean SPT and mean IgE levels significantly lower in OIT group	No safety data reported

DBPCFC, double-blinded, placebo-controlled food challenge; ED, Emergency Department; SPT, skin prick test.

concentrations. Some investigators have measured clinical efficacy as an increase in the median threshold amount of allergen tolerated in a DBPCFC at both baseline and at the end of treatment [21²²,24]. Alternatively some determined efficacy by a pass or fail determination, based on the ability to ingest a total fixed amount of allergen after the intervention period [20²²,22²²,23]. Reporting an 'increase in threshold' gives a more comprehensive picture than that of a simple 'pass or fail' determination, as even children who 'fail' a challenge may have shown a marked increase in threshold from their initial baseline challenge. Results have been also reported as 'full tolerance', which has been defined as an ability to ingest the entire challenge amount, or 'partial tolerance' if the child was able to ingest more than at baseline, but experienced allergic symptoms before completing the challenge [25,26].

Regardless of the varying protocols and allergens, all of these RCTs demonstrated an increase in threshold from baseline to the end of treatment in participants receiving OIT (Table 1). In the study by Skripak *et al.* [24], the median threshold dose of cow's milk tolerated significantly increased in the active group from 40 to 5140mg of protein after OIT, compared with no change in the placebo group. Additionally, the seven children in the placebo group went on to receive the active OIT treatment and achieved an increase in the median dose threshold from 40 to 8140mg. These findings are also consistent with Varshney *et al.*'s [21²²] study with peanut, in which there was an increase in the median threshold in the OIT group from 280 to 5000mg of protein (approximately 20 peanuts), compared with no increase in the placebo group. Despite these promising observations, a recent meta-analysis deemed there to be insufficient evidence to show any greater clinical benefit of OIT for patients compared with the use of a standard elimination diet [28²⁹]. In this meta-analysis however, there were only three RCTs available [24–26] that fit the inclusion criteria and these studies were greatly heterogeneous, making it difficult to provide any statistical significance.

The ultimate goal in the treatment of food allergy is to induce complete and 'permanent' immune tolerance to the food allergen, where the individual remains tolerant even after long allergen-free periods. Although OIT appears to be effective whilst the allergen is being consumed regularly, the long-term effects are still uncertain and likely to vary between individuals. Two of the aforementioned studies [20²²,26] investigated this by including an allergen-free period prior to the final OFC, addressing the question of efficacy with regard to

long-term immune tolerance. The study by Staden *et al.* [26] included a 4–6-week food allergen (cow's milk and egg) free period before the final OFC and demonstrated a lower efficacy rate than other studies, with only 9 of 25 (36%) children in the OIT group able to fully pass the OFC. Interestingly, there was no difference between intervention and control groups, as the control group also had 35% of children exhibiting total tolerance (fully passing the OFC). Burks *et al.* [20²²] also demonstrated a decrease in tolerance after an allergen-free period. After 22 months of egg OIT, 75% of children passed an OFC; however, after a further 2 months on an egg-free diet, this number dropped to 28%. This is consistent with the notion that OIT induces 'transient tolerance', whereby the tolerance state is maintained through regular oral ingestion of the allergen, but is not sustained with periods of allergen avoidance [29]. This however has not been studied extensively and more research is needed to assess the long-term efficacy of OIT.

The best age to commence OIT and the food allergens best targeted also require further investigation. Cow's milk and egg allergy are more prevalent in early childhood, yet also more transient as resolution is common with age [4,30]. This has led to questions about the timing and efficacy of OIT with cow's milk and egg, as it can be difficult to differentiate between the natural resolution and the active induction of tolerance by OIT. However, RCTs in which the intervention and control groups are age-matched should address this issue.

IMMUNOLOGICAL EVIDENCE FOR TOLERANCE INDUCTION FOLLOWING ORAL IMMUNOTHERAPY

Oral tolerance is described as an active immunological process to facilitate nonresponse to any antigen administered orally, and allergy reflects a breakdown of this process [31]. Allergen-specific immunoglobulins are well recognized markers reflecting the underlying cellular processes involved in the development of an allergic or tolerant phenotype. Most OIT studies have examined the changes in specific IgE and IgG4 in response to the treatment. As with many studies of subcutaneous immunotherapy, allergen-specific IgG4 has been a useful marker of the development of immune tolerance, without necessarily any sustained decline in IgE levels [32]. Whereas some studies observed that specific IgE levels decreased significantly after cow's milk and egg OIT [22²²,25,26], some of these saw the same pattern in the control group children who developed natural tolerance on an elimination diet [26]. Other studies reported no change in the IgE

levels in the OIT group from baseline or when compared to the control group [23,24].

Although specific IgE results are conflicting, changes in allergen-specific IgG4 are more consistent across the trials, with most showing significantly increased levels after OIT. Skripak *et al.* [24] saw an increase in the median cow's milk specific IgG4 of 767% in the treatment group compared with no change in the placebo group. Burks *et al.* [20²²] established that IgG4 levels were significantly higher in participants who were tolerant to egg than those children who reacted at all challenges ($P < 0.02$). Little is known about the mechanistic role of IgG4 in tolerance induction, but it is thought to interfere with IgE antigen binding [29]. More recently, the allergen-specific IgE-to-IgG4 ratio has been investigated in egg allergy as the best predictor for clinical reactivity and has been shown to be more effective than either IgE or IgG4 alone [33²]; however, this has not been reported as an outcome measure in any of the above-mentioned OIT trials.

THE SAFETY OF ORAL IMMUNOTHERAPY

OIT has shown promise in inducing tolerance in food allergic children, both clinically and immunologically; however, the safety of such treatment is still of concern and a key reason that this has not been translated into routine clinical practice. Most children receiving OIT have reportedly experienced allergic symptoms at some point during the treatment. The majority of these reactions occurred during the dose-escalation phase in hospital [20²²]. Most were mild-to-moderate symptoms and resolved spontaneously or with a dose of antihistamine. Minor cutaneous or abdominal reactions make up the bulk of the overall symptoms observed with OIT, but there have also been cases of serious adverse events including respiratory and systemic reactions requiring epinephrine. Nearly all of the serious adverse events occurred during the hospital visits and were treated by the medical staff; however, there were four cases that occurred at home in two of the cow's milk studies [24,25]. Three of these four doses were related to the OIT treatment; however, one case was in the control group because of accidental exposure [24].

As the inclusion criteria between these trials were heterogeneous, the overall risk associated with the allergen exposure varies with the population characteristics of the children enrolled. Although most studies excluded children with a history of a severe reaction or anaphylaxis, Longo *et al.* [25] enrolled severely cow's milk allergic children, of whom 78% had specific IgE levels above 100 kU/l, and also a history of at least one severe reaction to

cow's milk. As a result, this particular group of children experienced more adverse events than observed in other studies. Five doses of epinephrine were administered for serious reactions to OIT, which accounted for one-third of the total doses of epinephrine given across all the RCT OIT studies included in this review.

Adjunctive administration of recombinant monoclonal anti-IgE therapy may be a promising strategy to address some of the safety concerns associated with OIT [34²²]. This may be particularly useful during the early stages of OIT when reactions are most common and severe. The use of anti-IgE is expensive, but has been shown to be effective in reducing the number of severe allergic reactions during ragweed immunotherapy [35] and has also been used to reduce allergic symptoms observed during oral peanut challenges [36]. Research is ongoing to further explore this possibility.

Children with food allergies are at risk of an allergic reaction even on an elimination diet because of accidental exposure, and with the rise of processing in the food industry, it can be difficult to avoid the hidden allergens [37]. The increased risk of OIT when compared with a standard elimination diet is still uncertain, and more RCTs are needed on a larger scale for each particular allergen to deem whether this treatment is effective in a cost vs. benefit analysis. OIT dose escalations seem to induce the majority of allergic reactions and they are typically performed in a controlled environment, under the direct supervision of medical staff. This generally ensures the child is tolerant prior to home dosing, and even in the initial stages of these trials children are consuming more food allergen than they have previously, which could reduce the risk of a reaction because of accidental exposure.

Of concern for clinical practice is the somewhat unpredictable nature of immune tolerance, in which the immune responses and the threshold for reactivity can be affected by other factors such as infection and exercise [26]. It is therefore vital for all participants to have the necessary medication and auto-injectors at home, in case a previously tolerated dose causes a reaction when the immune system is compromised.

ALLERGEN EXPOSURE IN THE PRIMARY PREVENTION OF FOOD ALLERGY

There are currently a number of RCTs investigating the role of allergen exposure in the primary prevention of food allergies. These current trials (summarized in Table 2) are testing the hypothesis that early regular exposure to food allergens in infancy is more likely to induce oral tolerance, and reduce the risk of

Table 2. Current randomized controlled trials on food allergen exposure in infancy to prevent food allergy

Study	Study type (sample size)	Trial registration details	Population characteristics	Intervention	Comparison	Primary outcome
STAR (Australia) Optimal timing of solid food introduction to infants at high risk of developing allergic disease	Blinded, RCT (n = 86)	ACTRN 12609000415202 Date of trial registration 5/06/2009	High risk – infants with moderate-to-severe eczema	Daily consumption of egg powder from 4 months until 8 months of age. Cooked egg introduced from 8 months	Daily consumption of placebo, rice powder from 4 months until 8 months of age. Cooked egg introduced from 8 months	IgE-mediated egg allergy at 12 months of age based on positive SPT and egg challenge
STEP (Australia) Early regular egg exposure during infancy to prevent egg allergy	Blinded, RCT (n = 1512)	ACTRN 12610000388011 Date of trial registration 13/05/2010	Intermediate risk – maternal history of allergy + positive maternal SPT	Daily consumption of egg powder from 4 to 6 months until 10 months of age. Egg introduced from 10 months	Daily consumption of placebo, inge-matched rice powder from 4 to 6 months until 10 months of age. Egg introduced from 10 months	IgE-mediated egg allergy at 12 months of age based on positive SPT and egg challenge
BEAT (Australia) The effect of early introduction of egg in the diet of high risk for atopic infants and subsequent egg allergy	Blinded, RCT (n = 600)	ACTRN 12611000535976 Date of trial registration 24/05/2011	Intermediate risk – first-degree relative with atopy No infant IgE sensitization to egg at 4 months of age	Daily consumption of egg powder from 4–6 months until 12 months of age, with egg-free diet until 8 months, then introduction of unrestricted diet from 8 months	Daily consumption of placebo, rice powder from 4 to 6 months until 12 months of age, with egg-free diet until 8 months then introduction of unrestricted diet from 8 months	IgE sensitization to egg measured by SPT at 8 and 12 months of age
EAT (UK) Early introduction of allergenic foods to induce tolerance in infants	RCT (n = 2500)	ISRCTN 14254740 Date of trial registration 31/03/2009	Normal risk – general population	Exclusive breastfeeding until 3 months of age then sequential introduction of cow's milk, egg, wheat, sesame, fish and peanut from 3 months of age	Exclusive breastfeeding until around 6 months of age and no early introduction of allergenic foods before 6 months	Prevalence of IgE-mediated food allergy between 1 and 3 years of age, as defined by food challenge
LEAP (UK) Promoting tolerance to peanut in high-risk children	RCT (n = 640)	NCT00329784 Date of trial registration 23/05/2006	High risk – infant with eczema and egg allergy	Peanut consumption in the form of an age appropriate peanut snack commencing from 4 to 10 months of age	Peanut avoidance	Prevalence of clinically defined peanut allergy at 5 years of age
HEAP (Germany) Hen's Egg Allergy Prevention	RCT (n = 800)	Personal communication	Normal risk – general population	Egg powder 3 times a week from 4 to 6 months of age	Placebo powder 3 times a week from 4 to 6 months	IgE sensitization to egg at 12 months of age
PEAAD (Germany) Preventing Peanut Allergy in Atopic Dermatitis	Nonrandomized self-allocated controlled (n = 460)	Personal communication	High risk – eczema without peanut sensitization	Peanut snack 3 times a week from 5 to 30 months	Peanut avoidance	IgE-mediated peanut allergy after 1 year of consumption or avoidance
(Japan) Prevention of egg allergy in infants with atopic dermatitis	Blinded, RCT (n = 200)	JPRN-UMIN000008673 Date of trial registration 10/08/2012	High risk – infants with eczema	Daily consumption from 6 months of age of egg powder	Daily consumption from 6 months of age of placebo pumpkin powder	Negative egg food challenge at 1 year old

RCT, randomized controlled trial; SPT, skin prick test.

food allergy development, than avoidance or delayed exposure.

The majority of the current RCTs are investigating the timing of introduction to one specific food allergen, either hen's egg or peanut. However, the inclusion criteria differ among these trials (see Table 2), in which the risk of food allergy development is varied; high-risk infants with eczema are being investigated in Starting Time for Allergy Reduction (STAR), Learning Early About Peanut (LEAP) and Preventing Peanut Allergy in Atopic Dermatitis compared to intermediate-risk (family history of allergic disease) infants in Starting Time for Egg Protein (STEP) and Beating Egg Allergy Trial (BEAT). Additionally, some of the trials (e.g. BEAT and LEAP) are excluding infants with specific food allergen sensitization prior to randomization compared with other trials that are not (STAR and STEP). The Enquiring About Tolerance study in the United Kingdom is unique in investigating the intervention of exclusive breastfeeding until 3 months of age, then sequential introduction of cow's milk, egg, fish, wheat, sesame and peanut from 3 months of age compared with exclusive breastfeeding until around 6 months of age.

One of these RCTs, our own study investigating the role of early egg exposure in food allergy prevention (the STAR trial) is now complete and the results have been submitted for publication. One particularly interesting finding from this trial was that a significant proportion of high-risk infants with eczema already had established food sensitization and clinical reactivity (including anaphylaxis) prior to the introduction of solid foods at 4–5 months of age. This indicates that the processes leading to food allergen sensitization are already strongly established by this age in some infants, and that even earlier preventive interventions will ultimately be required. This underscores the pressing need to better define the events around much earlier to the food allergen encounter and it is essential to have a better understanding of the antecedent events that lead to the establishment of food allergy so early in infancy.

In the primary prevention of food allergy, exposure to 'food allergens' is only one component of a much bigger story, in which optimizing conditions during early critical periods of immune programming is vital to promote oral tolerance induction. The dose, timing and delivery method of the food allergen require investigation in tandem with other strategies that promote tolerogenic conditions such as optimizing early gut colonization, nutritional patterns and reducing exposure to pro-inflammatory factors.

CONCLUSION

Prevention strategies are of prime importance as rates of food allergies in children continue to increase. The results of current RCTs investigating the early regular exposure to food allergens in infancy for the primary prevention of food allergy are eagerly awaited. For the treatment of established food allergy, more studies are needed in relation to each of the specific food allergens in order to adequately assess both the efficacy and safety of food allergen exposure. Adjunctive administration of anti-IgE therapy with OIT may be a way forward to address the safety concerns associated with 'intentional' allergen exposure. Recent studies are adding to a body of growing evidence that exposure may be a better alternative to avoidance; however, at this point, there is not enough evidence available for a shift in the current, routine clinical practice.

Acknowledgements

None.

Conflicts of interest

The authors declare that no financial or other conflict of interest exists in relation to the content of the article.

The authors are supported by the project grants from the Australian National Health and Medical Research Council, Australia.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

■ of special interest

■ of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 319–320).

1. Osborne NJ, Koplin JJ, Martin PE, *et al.* Prevalence of challenge-proven IgE-mediated food allergy using population-based sampling and predetermined challenge criteria in infants. *J Allergy Clin Immunol* 2011; 127:668–676. e1–e2.
2. Mullins RJ. Paediatric food allergy trends in a community-based specialist allergy practice, 1995–2006. *Med J Aust* 2007; 186:618–621.
3. Chen J, Hu Y, Allen KJ, *et al.* The prevalence of food allergy in infants in Chongqing, China. *Pediatr Allergy Immunol* 2011; 22:356–360.
4. Savage JH, Matsui EC, Skripak JM, Wood RA. The natural history of egg allergy. *J Allergy Clin Immunol* 2007; 120:1413–1417.
5. Fleischer DM, Perry TT, Atkins D, *et al.* Allergic reactions to foods in preschool-aged children in a prospective observational food allergy study. *Pediatrics* 2012; 130:e25–e32.
6. Flokstra-de Blok BMJ, Dubois AEJ, Vlieg-Boerstra BJ, *et al.* Health-related quality of life of food allergic patients: comparison with the general population and other diseases. *Allergy* 2010; 65:238–244.
7. Kulis M, Burks AW. Oral immunotherapy for food allergy: clinical and preclinical studies. *Adv Drug Deliv Rev* 2012. <http://dx.doi.org/10.1016/j.addr.2012.10.004>.
8. Oppenheimer JJ, Nelson HS, Bock SA, *et al.* Treatment of peanut allergy with rush immunotherapy. *J Allergy Clin Immunol* 1992; 90:256–262.
9. Nelson HS, Lahr J, Rule R, *et al.* Treatment of anaphylactic sensitivity to peanuts by immunotherapy with injections of aqueous peanut extract. *J Allergy Clin Immunol* 1997; 99 (6 Pt 1):744–751.
10. Poisson A, Thomas G, Jean-Landais N, Giafre E. Rapid acquired tolerance to cow's milk by oral route in a case of severe childhood food allergy. *Allergy Immunol* 1988; 20:67–68.

11. Bauer A, Ekanayake Mudiyanse S, Wigger-alberti W, Elsner P. Oral rush desensitization to milk. *Allergy* 1999; 54:894–895.
12. Patriarca C, Romano A, Venuti A, *et al.* Oral specific hyposensitization in the management of patients allergic to food. *Allergol Immunopathol* 1984; 12:275–281.
13. Patriarca G, Schiavino D, Nucera E, *et al.* Food allergy in children: results of a standardized protocol for oral desensitization. *Hepatogastroenterology* 1998; 45:52–58.
14. Meglio P, Bartone E, Plantamura M, *et al.* A protocol for oral desensitization in children with IgE-mediated cow's milk allergy. *Allergy* 2004; 59:980–987.
15. Buchanan AD, Green TD, Jones SM, *et al.* Egg oral immunotherapy in nonanaphylactic children with egg allergy. *J Allergy Clin Immunol* 2007; 119:199–205.
16. Jones SM, Pons L, Roberts JL, *et al.* Clinical efficacy and immune regulation with peanut oral immunotherapy. *J Allergy Clin Immunol* 2009; 124:292–300; 300.e1–e97.
17. Blumchen K, Ulbricht H, Staden U, *et al.* Oral peanut immunotherapy in children with peanut anaphylaxis. *J Allergy Clin Immunol* 2010; 126: 83.e1–91.e1.
18. García Rodríguez R, Urrea JM, Feo-Brito F, *et al.* Oral rush desensitization to egg: efficacy and safety. *Clin Exp Allergy* 2011; 41:1289–1296.
19. Patriarca G, Nucera E, Roncallo C, *et al.* Oral desensitizing treatment in food allergy: clinical and immunological results. *Aliment Pharmacol Ther* 2003; 17:459–465.
20. Burks AW, Jones SM, Wood RA, *et al.* Oral immunotherapy for treatment of egg allergy in children. *N Engl J Med* 2012; 367:233–243.
 Most recently, Burks *et al.* published a randomized placebo-controlled trial investigating OIT in egg allergic children. This study involved a staged OFC protocol in which children were challenged at three time points. They demonstrated that egg OIT is most effective (75% of patients) after 22 months of desensitization and when there has not been an 'allergen-free' period. With no serious adverse events, this study is an advocate for both safety and efficacy of OIT in the treatment of egg allergic patients.
21. Varshney P, Jones SM, Scurlock AM, *et al.* A randomized controlled study of peanut oral immunotherapy: clinical desensitization and modulation of the allergic response. *J Allergy Clin Immunol* 2011; 127:654–660.
 This is the first randomized, placebo-controlled trial investigating peanut OIT as a treatment for peanut allergic children. In this study after 44 weeks of desensitization, 16 of 19 patients were able to consume the equivalent of 20 peanuts, compared with the control group, who could only tolerate 1 peanut. Unfortunately, because of a significant difference in the OFC outcomes between the groups, this study was terminated prematurely and they were not able reach their target of 60 children. However, this level of desensitization is an advance in the treatment of peanut allergy and has the potential to decrease the potential severe reactions due to accidental exposure.
22. Martorell A, De la Hoz B, Ibáñez MD, *et al.* Oral desensitization as a useful treatment in 2-year-old children with cow's milk allergy. *Clin Exp Allergy* 2011; 41:1297–1304.
 Martorell *et al.* enrolled 60 cow's milk allergic infants between the age of 24 and 36 months for this OIT study. Although many other cow's milk OIT studies include infants as young as 1 year of age, this study is the first with infants in a tight age range. This trial found a desensitization rate of 90% after 1 year of OIT.
23. Pajno GB, Caminiti L, Ruggeri P, *et al.* Oral immunotherapy for cow's milk allergy with a weekly up-dosing regimen: a randomized single-blind controlled study. *Ann Allergy Asthma Immunol* 2010; 105:376–381.
24. Skripak JM, Nash SD, Rowley H, *et al.* A randomized, double-blind, placebo-controlled study of milk oral immunotherapy for cow's milk allergy. *J Allergy Clin Immunol* 2008; 122:1154–1160.
25. Longo G, Barbi E, Berti I, *et al.* Specific oral tolerance induction in children with very severe cow's milk-induced reactions. *J Allergy Clin Immunol* 2008; 121:343–347.
26. Staden U, Rolinck-Werninghaus C, Brewe F, *et al.* Specific oral tolerance induction in food allergy in children: efficacy and clinical patterns of reaction. *Allergy* 2007; 62:1261–1269.
27. Morisset M, Moneret-Vautrin DA, Guenard L, *et al.* Oral desensitization in children with milk and egg allergies obtains recovery in a significant proportion of cases: a randomized study in 60 children with cow's milk allergy and 90 children with egg allergy. *Eur Ann Allergy Clin Immunol* 2007; 39:12–19.
28. Fisher HR, Toit GD, Lack G. Specific oral tolerance induction in food allergic children: is oral desensitisation more effective than allergen avoidance? *Arch Dis Child* 2011; 96:259–264.
 This meta-analysis is a comprehensive summary of the literature available on RCTs in OIT prior to 2011. The inclusion criteria required a DBPCFC at baseline to determine true food allergy and also the assessment of tolerance/allergy using an OFC or DBPCFC at the completion of OIT. Therefore, it only includes three of the RCTs we have mentioned in this review.
29. Rachid R, Umetsu D. Immunological mechanisms for desensitization and tolerance in food allergy. *Semin Immunopathol* 2012; 34:689–702.
30. Skripak JM, Matsui EC, Mudd K, Wood RA. The natural history of IgE-mediated cow's milk allergy. *J Allergy Clin Immunol* 2007; 120:1172–1177.
31. Ko J, Mayer L. Oral tolerance: lessons on treatment of food allergy. *Eur J Gastroenterol Hepatol* 2005; 17:1299–1303.
32. Ozdemir C, Kucuksezer UC, Akdis M, Akdis CA. Mechanisms of immunotherapy to wasp and bee venom. *Clin Exp Allergy* 2011; 41:1226–1234.
33. Okamoto S, Taniuchi S, Sudo K, *et al.* Predictive value of IgE/IgG4 antibody ratio in children with egg allergy. *Allergy Asthma Clin Immunol* 2012; 8:9.
 This recent study examined the role of allergen-specific immunoglobulin (specifically IgE and IgG4) in predicting the clinical reactivity in egg allergic children. Their results show that the IgE/IgG4 ratio is a significantly better predictor of challenge outcomes than either IgE or IgG4 alone. These results could lead towards better interpretation of immunological markers for the development of oral tolerance.
34. Lieberman J, Chehade M. Use of omalizumab in the treatment of food allergy and anaphylaxis. *Curr Allergy Asthma Rep* 2013; 13:78–84.
 This is a recent and comprehensive review about the potential use of anti-IgE therapy in food allergy. Of particular interest is the notion that anti-IgE therapy when used in conjunction with OIT may allow safer administration of allergen and decrease the risk of severe allergic reactions.
35. Casale TB, Busse WW, Kline JN, *et al.* Omalizumab pretreatment decreases acute reactions after rush immunotherapy for ragweed-induced seasonal allergic rhinitis. *J Allergy Clin Immunol* 2006; 117:134–140.
36. Leung DYM, Sampson HA, Yunginger JW, *et al.* Effect of anti-IgE therapy in patients with peanut allergy. *N Engl J Med* 2003; 348:986–993.
37. Yu JW, Kagan R, Verreault N, *et al.* Accidental ingestions in children with peanut allergy. *J Allergy Clin Immunol* 2006; 118:466–472.