Specific oral tolerance induction in food allergic children: is oral desensitisation more effective than allergen avoidance?

A meta-analysis of published RCTs

H R Fisher, G du Toit, G Lack

Division of Asthma, Allergy and Lung Biology, MRC and Asthma UK Centre in Allergic Mechanisms of Asthma, Guy's and St Thomas' NHS Foundation Trust, King's College London, London, UK

Correspondence to
Helen R Fisher, Health and Social Care Research, 9th Floor, Capital House, 42 Weston Street, London SE1 3QD, UK; Helen.r.fisher@kcl.ac.uk

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ABSTRACT

Objective To determine whether specific oral tolerance induction (SOTI) is more effective than avoidance in inducing tolerance in children aged 0–18 years who have immunoglobulin E (IgE)–mediated food allergy.

Data sources MEDLINE (1950 to July 2009), EMBASE (1980 to July 2009) and all EBM Reviews: Cochrane Database of Systematic Reviews, ACP Journal Club, Database of Abstracts of Reviews of Effects, Cochrane Methodology Register, Health Technology Assessment and NHS Economic Evaluation Database (from start date to November 2008). The online table of contents (November 2003 to July 2009) of the *Journal of Allergy and Clinical Immunology, Pediatric Allergy and Immunology* and *Allergy* were also searched, and reference lists of retrieved articles were scrutinised for relevant studies.

Study selection Randomised controlled trials (RCT) were included providing they enrolled children with IgE-mediated food allergy diagnosed using the criterion standard tool (double-blind placebo-controlled food challenge) before randomisation and also compared posttreatment tolerance between groups using the criterion standard measures.

Results Three studies met the inclusion criteria, and two proved a statistically significant reduction in endpoint allergy (determined by oral food challenge) after SOTI compared with the control. The meta-analysis of the included studies found a lower RR of allergy after SOTI, but this did not meet statistical significance (0.606783; 95% CI 0.317733 to 1.158791).

Conclusions SOTI cannot yet be recommended in routine practice as a means to induce tolerance in children with IgE-mediated food allergy. Further research is needed using large, high-quality RCT that investigate a variety of food allergens and assesses the long-term efficacy, safety and cost-effectiveness of SOTI.

What is already known on this topic

- IgE-mediated food allergy, a relatively common childhood condition for which there is currently no cure, poses a significant psychological and financial burden on children, families and society.

What this study adds

- SOTI to foods is a potentially important new treatment for IgE-mediated food allergy.
- Further high-quality RCTs that evaluate the efficacy of SOTI to a variety of foods, establish the long-term immunomodulatory effect of the treatment and consider the cost-effectiveness of this therapy are required.

IgE-mediated food allergy is an adverse reaction to food that is reproducible under blinded conditions.[1] The prevalence of IgE-mediated food allergy in children is estimated to be between 1.6% and 6%,[2–7] and there is currently no treatment; hence, children must carry emergency medications and practice strict avoidance of the offending food.[8] However, accidental exposures still occur, often in the home during the course of everyday life,[6] triggering allergic reactions that frequently require medical treatment and which, if severe, may even lead to death. Indeed, six deaths from food allergy were recorded in children in the UK in 2006,[9] and this may be an underrepresentation due to difficulties in diagnosis and during postmortem.[10]

Food allergy poses a significant psychological burden; studies have found that families with food-allergic children have reduced quality of life[11] and are more anxious about their condition than those with insulin-dependent diabetes mellitus.[12] Additionally, the current financial burden of food allergy is substantial,[13] with costs being incurred by the health service, food industry, employers, consumers, carers and regulatory bodies.[14]

Although food allergy, particularly cow's milk and hen's egg allergies, may resolve spontaneously in some children, many continue to be allergic into adulthood.[15] Given the associated physical, psychological and financial burdens of persistent IgE-mediated food allergy, there is a need to uncover a cure. Oral desensitisation, also referred to as immunotherapy and, more recently, specific oral tolerance induction (SOTI), is the induction of tolerance through immune modulation that is achieved through incremental exposure to the relevant allergen.[8] Although no discipline-agreed definition of tolerance exists, it is generally said to have been achieved when an age-appropriate portion of

food can be consumed without the demonstration of allergic symptoms. However, some allergists believe that children should only be labelled "truly tolerant" after SOTI if tolerance is demonstrated after a secondary elimination of the allergen.[16] This demonstrates that the immunomodulatory effect is sustained and not due to transient tolerance, that is, tachyphylaxis that is only maintained though continuous exposure.

The concept of desensitisation is not new. Efficacy in tolerance induction against airborne allergies, via both sublingual and subcutaneous routes, has been proved by two Cochrane reviews,[17 18] and subcutaneous desensitisation to foods has also been trialled but was discontinued on safety grounds.[19] However, the literature carries case reports of successful SOTI to foods, the first in 1908[20] with more being published more recently.[21–23] Furthermore, SOTI to foods has proved successful in murine models.[24] In this context, we sought to examine whether SOTI to foods was more effective than avoidance in the development of oral tolerance through a meta-analysis of relevant randomised controlled trials (RCT).

METHODOLOGY OF THE REVIEW

The inclusion/exclusion criteria

The a priori determined inclusion criteria for this review stipulated that studies must have

1. included children aged 0–18 years with IgE-mediated food allergy proven by double-blind placebo-controlled food challenge (DBPCFC) at the start of the study;
2. assessed the success of SOTI using the outcome measure of tolerance/allergy;
3. objectively assessed this outcome using oral food challenge or DBPCFC for tolerance but DBPCFC for allergy
4. scored ≥1+ using the National Institute for Health and Clinical Excellence (NIHCE)[25] criteria for quality assessment;
5. been written in the English language.

The diagnosis of IgE-mediated food allergy is complicated and sometimes transient.[26] Although two surrogate markers for the diagnosis of food allergy exist, neither skin prick testing nor specific-IgE testing can unequivocally determine IgE-mediated food allergy, even when used in combination.[27] Hence, the criterion standard diagnostic modality remains the oral food challenge. To minimise bias from the inclusion of non-allergic children or misdiagnosis of end point, studies that did not use the criterion standard food challenges to assess allergic status at study inclusion and end point were excluded. Studies that included children with non–IgE-mediated allergy were also excluded because the disease process and treatment of this condition differs from that of IgE-mediated allergy, as were studies that included adults if extraction of data relating to children was not possible. Data that were published more than once were only included once. Consideration was given as to whether studies that did not blind the treatment and control groups should be included. Blinding within SOTI is currently under debate. Some suggest it is essential to ensure the rigour of the study.[16] However, others believe that because of difficulties finding a placebo that mimics the symptoms experienced during SOTI and the risk that children will falsely believe they are tolerant and so alter their behaviour regarding avoidance of the relevant food that may result in an allergic reaction, this is not practical or ethical.[28] For the purposes of this meta-analysis, lack of blinding was not an exclusion criterion.

Search strategy

One author (HF) conducted the search. The Cochrane Database of Systematic Reviews was first examined using the term *food allergy*, but no relevant review was found. Using the terms detailed in table 1, a variety of additional electronic databases were searched: MEDLINE (1950 to July 2009), EMBASE (1980 to July 2009) and all EBM Reviews: Cochrane Database of Systematic Reviews, ACP Journal Club, Database of Abstracts of Reviews of Effects, Cochrane Methodology Register, Health Technology Assessment and NHS Economic Evaluation Database (from start date to November 2008). To further improve the sensitivity of the search, the online table of contents of three key specialty journals (*Pediatric Allergy*, the *Journal of Allergy and Clinical Immunology* and *Allergy*) were scrutinised (November 2003 to July 2009), and reference lists of retrieved articles were also examined for relevant studies.

Once results were returned, titles and abstracts were examined. For those considered likely to be primary research, full-text articles were gathered and checked against the inclusion criteria. Figure 1 describes the flow of studies through the stages.

Study type and quality criteria

One author (HF) reviewed the studies using the NIHCE quality framework,[25] which permitted the assessment of the quality of the randomisation, the degree of matching between groups, the follow-up rates of the studies and the statistical methodologies used. This ensured that included studies were well conducted, with a low risk of bias and high probability that any noted relationship is causal. This promoted the validity of the meta-analysis.

Data synthesis

As the aim was to establish whether SOTI is more effective than avoidance in achieving tolerance in children with IgE-mediated food allergy, the number of endpoint tolerant children in each group was considered the most suitable criteria for comparison. Whereas some studies assessed the outcome of the treatment using both challenge-proven allergy and indicators of sensitisation such as skin prick testing, specific-IgE and total-IgE quantification, this review does not consider the effect of SOTI on the indicators of sensitisation.

The pooled odds ratio and 95% confidence interval (CI) were calculated using StatsDirect V.2.7.2 (9 June 2008) to establish the risk ratio (RR) of allergy after SOTI assessed using criterion standard tools. As meta-analyses introduce heterogeneity due to inherent differences in included studies,[29] a random effects model that calculates heterogeneity[30] was used.

RESULTS

Findings of the review

After completing the literature review and assessing the articles against predetermined criteria, 15 studies were found,

Table 1 Facet analysis

MeSH terms		Synonyms
Food hypersensitivity		Food allergy
Infant, child—preschool, child, adolescent	OR	Child
Desensitisation, immunologic		Oral immunotherapy
		SOTI

MeSH, Medical Subject Headings.

of which 12 were either case series or controlled studies. However, three RCTs were found,[31–33] and all of these met the additional inclusion criteria.

The main characteristics of the three included studies may be seen in table 2. Two studies were conducted in Europe[31 32] and one in the USA.[33] One study[31] included infants as young as 6 months, and all studies had a higher proportion of males than females, which is representative of the general population of allergic children.[34] All the studies examined the effect of oral tolerance induction to cow's milk protein, with one study[32] enrolling children who were exquisitely sensitive, reacting at <1 ml of whole cow's milk at the start of the study. One study also performed oral tolerance induction to hen's egg, although each child was desensitised to only one food (cow's milk or hen's egg) during the study.[31]

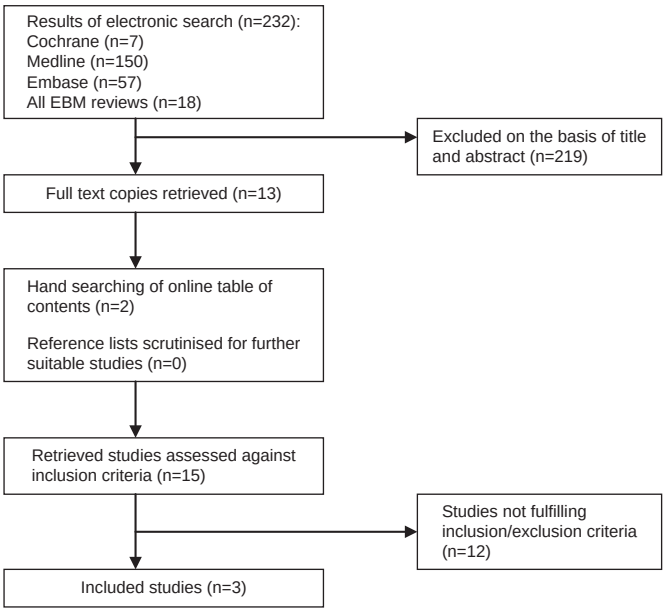

Figure 1 Flow of studies through review stages.

In two studies,[31 32] children who were not randomised to receive SOTI practiced avoidance of the relevant allergen. Children in the third study[33] consumed a placebo, although no details of the substance used for the placebo were provided.

Treatment dosing schedules varied between studies, with two using an initial rush phase, conducted in a hospital setting, during which children were given incremental doses of the relevant allergen at 1 h[32] or 30 min[33] intervals. An updosing phase, in which the dose was increased according to the relevant protocol on a daily basis until the top dose of the protocol had been achieved, was subsequently administered at home by the parents of the children. Children were then maintained on the relevant dose, consuming this daily for a mean of 13[33] and 42[32] weeks before the final evaluation of the efficacy of the treatment by oral food challenge in a hospital setting. The third study[31] did not include a rush phase, and children in the treatment arm were updosed by parents at home on a daily basis until the top dose of the protocol was reached, after which they consumed the dosage daily for 7–15 months. Children on this protocol[31] discontinued their consumption of the relevant food for 2 months before re-evaluation by oral food challenge in a hospital setting, thereby examining the permanent immunomodulatory effect of the treatment.

Table 2 Main characteristics of included studies

Study (year)	Evidence level (NIHCE 2007)	n	Age range (years)	Male, n (%)	Design (country of origin)	Groups (n)	Food	Dosing regime/ washout before evaluation	Top dose used in maintenance	Main outcome	Tools used to measure main outcome	Additional outcome measures
Staden *et al*[31]	1+	47	0.6–12.9 (me=2.5)	29 (62)	RCT (Germany)	Treatment (25)	Cow's milk or hen's egg	R=none U=67days M=7–15 months	8250 mg cow's milk 2800 mg Hens egg	Tolerance of age-appropriate portion of relevant food	DBPCFC (both groups)	Before/after total IgE Before/after specific IgE Adverse reactions
						Avoidance (20)		2-month washout				
Longo *et al*[32]	1+	60	5–17 (m=7.9 SOTI, m=8.1 avoidance)	39 (65)	RCT (Italy)	Treatment (30)	Cow's milk	R=10 days U=65 days M=42 weeks	150 ml cow's milk	Tolerance of age-appropriate portion of relevant food	OFC (if tolerance suspected) DBPCFC (where allergy suspected)	Partial* tolerance Before/after specific IgE Adverse reactions
						Avoidance (30)		No washout				
Skripak *et al*[33]	1++	20	6–17 (m=9.3 SOTI, m=10.2 placebo)	12 (60)	Double-blind RCT (USA)	Treatment (13)	Cow's milk	R=1 day U=8–16 weeks M=13 weeks	500 mg cow's milk	Tolerance of age-appropriate portion of relevant food	DBPCFC (both groups)	Before/after total IgE Before/after specific IgE Before/after IgG Before/after IgG4
						Placebo (7)		No washout				Before/after SPT

*M, maintenance; m, mean; me, median; OFC, oral food challenge; R, rush phase; SPT, skin prick testing; U, updosing.
* Children who were able to drink at least 5 ml but <150 ml of milk during the final oral food challenge were deemed partially tolerant.

Table 3 Results of studies included in review

Study	Number lost to follow-up	Results after SOTI (%)	Results after avoidance (%)	Statistical analysis
Staden *et al*[31]	2 (1 In each group)	Tolerant 9 (36) Allergic$_{[2.3}$ 16 (64)†	Tolerant 7 (35) Allergic 13 (65)	χ^2=0.005; p=0.944*
Longo *et al*[32]	0	Tolerant 11 (36) Allergic 19 (64)	Tolerant 0 (0) Allergic 30 (100)	χ^2 p=<0.001
Skripak *et al*[33]	1 (Treatment group)	Tolerant 12 (92) Allergic 1 (8)	Tolerant 0 (0) Allergic 7 (100)	Fisher exact test p=0.0003

*Figures were calculated for this review using results from study reports.
†Original results for children who underwent treatment showed that 9 (36%) children were challenge-proven tolerant, although 3 (12) responded to treatment with regular intake, and 4 (16%) partially responded (could tolerate a higher dose than at the initial challenge); for the purposes of this review, these children were deemed allergic and were grouped with the 9 (36%) other children who showed no response during the final challenge.

Table 4 RR of allergy post SOTI

Study	RR	95% CI	% Weight (random effects)
Staden *et al*[31]	0.984615	0.631465 to 1.580384	40.797322
Longo *et al*[32]	0.639344	0.461756 to 0.806964	45.934835
Skripak *et al*[33]	0.114286	0.014601 to 0.371939	13.267843

While the protocols of all the studies attempted a daily updosing schedule, the parents of the children who experienced more than mild symptoms during this phase were advised to contact the investigators before increasing the dose further, and schedules were individually amended to step down a dose, to remain on the same dose for an additional time period, to increase the dose but with smaller increments or to discontinue SOTI.

All the studies reported that children frequently experienced symptoms of an allergic reaction during the rush/updosing phases, most being mild to moderate—for example, urticaria, exacerbation of eczema and/or oral tingling, although more severe cardiorespiratory symptoms did occur, and intramuscular epinephrine was required by four children in the treatment group of one study.[33] Within the treatment arm of the study that enrolled children who were exquisitely sensitive to cow's milk,[32] four children during the rush (in hospital) phase and one child during the updosing (at-home) phase of the protocol required intramuscular epinephrine. Only one study[32] predosed children with antihistamine during the rush/updosing phases.

The treatment appeared acceptable to children and their families, with one study achieving a 100% follow-up rate.[32] However, in one study, one child withdrew from the treatment arm because of persistent reactive symptoms,[33] and in another[31] two children withdrew, one in each group, before study treatment commencing.

Results of the meta-analysis

The results of the individual studies may be seen in table 3. All the studies found tolerance more likely to occur after SOTI than avoidance/placebo, with differences universally meeting statistical significance. However, one[31] used the definition "any tolerance" rather than challenge-proven tolerance when performing statistical analysis. As raw data regarding tolerance assessed using criterion standard tools were available, the figures from this study[31] were analysed using χ^2 in SPSS for Windows V.16, and no significant difference was found between the treatment and avoidance groups (χ^2=0.005; p=0.944).

The RR of allergy after SOTI when compared with avoidance of the relevant food of each individual study may be seen in table 4, and two studies[32 33] showed that SOTI statistically significantly lowered the risk of allergy when compared with avoidance.

The forest plot in fig 2 shows the combined RR of allergy after SOTI. Although a reduction in allergy after treatment is highlighted, this fails to meet statistical significance (0.606783; 95% CI 0.317733 to 1.158791), and this is corroborated by a non-significant result for the combined χ^2 test that the RR differs from 1 (χ^2=2.29; p=0.1302). Cochran Q (8.87; p=0.0118) and I^2 (77.5%; 95% CI 0% to 91%) found high heterogeneity between studies, which further reduces the significance of findings.

DISCUSSION

In this meta-analysis of RCT in which the efficacy of SOTI to foods in achieving oral tolerance was compared with the current treatment of strict food avoidance, no difference could be established between the children receiving SOTI and those practising avoidance of the relevant food. However, this meta-analysis included only three studies with a total combined sample of only 127 children, which may have resulted in a type 2 error when considering statistical significance of results.[35] The studies were also found to be significantly heterogeneous, which may also account for this failure.

The significant heterogeneity may be explained by differences in protocols, countries of origin of research and by the inclusion of one study[31] that enrolled younger children than the other studies, performed SOTI to both cow's milk protein and hen's egg and assessed the efficacy of treatments after a period of secondary elimination of the relevant food. As this study contributed to 40% of the meta-analysis, its inclusion may account for the non-significant findings of the meta-analysis. However, in many ways, this study[31] is highly representative of the population of food allergic children; milk and egg allergy predominantly affect children aged <5 years,[36] and the use of a washout period before re-evaluation of allergic status may mimic more closely real life; few children will consume a particular food everyday. Indeed the literature carries case reports of loss of tolerance[37] and of exercise-induced anaphylaxis during/after SOTI[38 39]; hence, although two studies[32 33] within this review found that statistically more children were able introduce cow's milk into their diet after SOTI than those in the control arms, as neither study assessed whether tolerance persisted after secondary elimination, as yet, the long-term effects of SOTI appear variable.

An additional limitation of this review is that the included studies performed SOTI only to cow's milk or hen's egg, and although these are the most common childhood food allergens, they have historically been considered to be the most frequently outgrown,[40] although this view has recently been challenged.[41 42] However, no RCT of SOTI to alternative

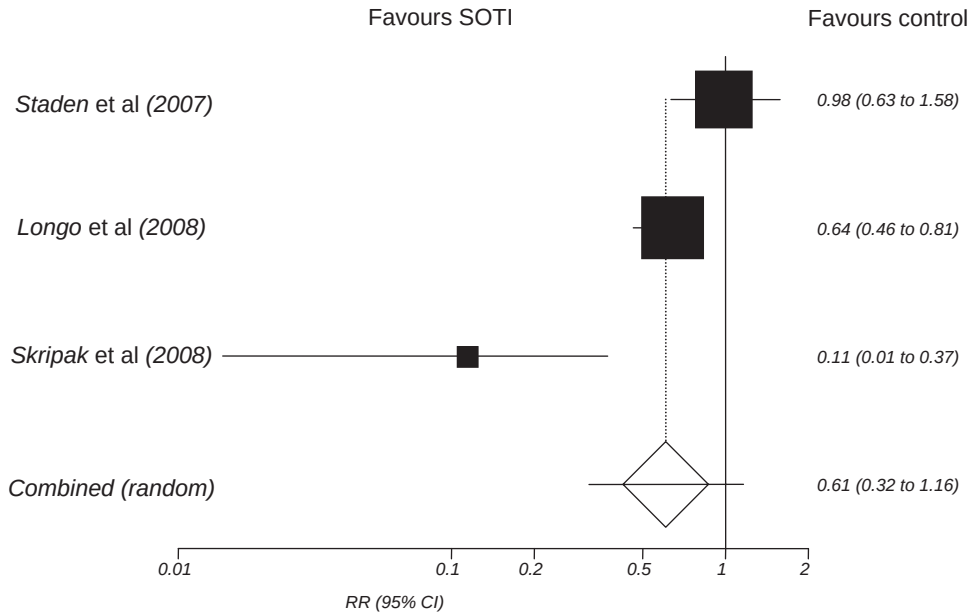

Figure 2 Meta-analysis of RR of allergy after treatment (random effects).

foods that related to children were found, although the recent literature does carry case series of successful SOTI to peanut.[43 44]

While this meta-analysis just failed to prove that SOTI is more successful than avoidance in the development of tolerance in food-allergic children, the need to find a treatment for IgE-mediated food allergy persists. Although trials of a drug that increase threshold of reactivity are ongoing,[45] SOTI appears to be the concept that currently offers most chance of a cure. However, further research is needed in a variety of areas before SOTI can be recommended for routine practice. Although SOTI seemed to increase the threshold of reactivity for many children, only a few were able to consume an age-appropriate portion of the relevant food, and fewer children attempted to liberalise their diet beyond the dose required by the study protocol, a situation that would more closely mimic real life, where children who are tolerant of a food can consume extremely large quantities of it without the demonstration of allergic consequences. When also considering the case reports of loss of tolerance after SOTI, further studies are needed on the long-term effects of this treatment. This review did not consider issues of safety and tolerability, and although all studies had good follow-up rates suggesting that SOTI was acceptable to the included children and their families, children in all the studies experienced allergic symptoms while undergoing SOTI. Although this was an anticipated adverse effect of this treatment and for many children, these symptoms were mild (perioral itching or skin reactions for example), some children experienced more concerning reactions including gastroenterological or respiratory symptoms. Indeed, two studies[32 33] reported use of epinephrine both during the inhospital induction phase and, more worryingly, in two instances, at home. Although SOTI may be acceptable to children and parents, further studies on the safety of this treatment are needed.

No single protocol exists for SOTI to foods; hence, as yet, the costs of this treatment are unknown. However, as large proportions of the three treatment protocols were performed at home by families with access to an on-call allergist, the clinical costs may not be prohibitive. Indeed, if clinical effectiveness was proven and, after more extensive investigation, the safety of SOTI was shown to be satisfactory, then, given the current financial burden of food allergy on society, SOTI may be a cost-effective and realistic intervention where no current treatment exists. Although this meta-analysis is not able to make recommendations for clinical practice, it has uncovered the need for further RCTs that conduct SOTI to a variety of food allergens and assess the long-term efficacy, safety and cost-effectiveness of this exciting and potentially important treatment for children with IgE-mediated food allergy.

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Competing interests GL has provided consultation for the advisory board for Synovate, Novartis and ALK-Abelló; provided academic lectures for SHS Nutricia, Nestlé and SHS International; received research support from the Immune Tolerance Network, the National Peanut Board, the Food Standards Agency, the Medical Research Council, the Food Allergy and Anaphylaxis Network and the Food Allergy Initiative and served as a scientific advisor for the Anaphylaxis Campaign and the National Peanut Board. The additional authors declare they have no competing interests.

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