A REVIEW OF THE INDUCTION OF TOLERANCE OF IgE-MEDIATED FOOD ALLERGY – PAST, PRESENT AND FUTURE

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ABSTRACT
This article reviews the recent advances and current state of equipoise in the use of immunotherapy for IgE-mediated food allergy. It examines the various methods currently under evaluation for induction of desensitisation and tolerance in food allergy and encompasses permissive diets which allow for inclusion of extensively heated food allergens, specific oral tolerance induction (SOTI), the use of adjuvants for specific tolerance induction and novel pharmacotherapies.

THE PAST-FOOD ALLERGY A RARE MEDICAL ODDITY
The idea of induction of tolerance in food allergy by oral immunotherapy, and the understanding that transient desensitisation and permanent tolerance are quite different, is not new. In 1939, almost 80 years ago, Gert Sydow published a case series of children who most likely had IgE-mediated cow’s milk allergy.1 He showed that children with allergy to cow’s milk (CM) could be rendered “insensitive” to the effects of CM if they were exposed at regular and increasing doses of CM. He also reported that whilst temporary tolerance was achievable, long term tolerance was not always possible. Furthermore, he reported that CM could be modified by heating, rendering it non-allergic in some children. This was before the discovery of the elusive “reaginie antibody” IgE, in 1966, and before the understanding of what constituted an allergen and how it might be modified in tertiary structure by heat or enzymatic processing. Food allergy, in 1939, was a rare medical oddity, not the epidemic it is today, and as with many insights in medicine, this approach to food allergy was not widely embraced at the time. Thus, this oral approach to desensitisation for food allergy was lost, only to reappear in the first two decades of the next century.

THE PRESENT
The prevalence of IgE-mediated food allergy has alarmingly and dramatically increased over the last 30 years. Whilst the highest rates are reported in countries such as Australia, the UK and USA2, there is good evidence to suggest a rise occurring in countries in transition, such as Asia and Africa.3 Along with this rapid increase in the food allergy has come a demand for services which are currently unmet. This has fostered desire to rethink late 20th century food allergy management of strict avoidance and monitoring for natural tolerance, to interventions which offer the hope of changing natural history and of inducing lifelong tolerance to food allergens in food allergic individuals.

EXTENSIVELY HEAT-TREATED ALLERGENS AND PERMISSIVE ALLERGEN EXPOSURE
In concert with the re-imagining of immunotherapy for food allergy, there has been a paradigm shift in management of food allergy over the last two decades. The previous mantra of strict avoidance of the food allergen has been increasingly challenged. Until recently, most allergy guidelines recommended strict avoidance of all forms and amounts of allergen for the diet of allergic children. This was partly on the basis of safety and also on the belief that accidental allergen exposure may delay the onset of tolerance.4 It is now widely held that this is unlikely to be the case, with a series of publications demonstrating that the majority of children allergic to hen’s egg and CM can tolerate extensively heated egg and CM in serving size quantities.

WHAT ARE THE POTENTIAL BENEFITS OF PERMISSIVE ALLERGEN EXPOSURE IN CHILDREN WITH IgE-MEDIATED ALLERGY TO EGG AND CM?
There are potential positive effects which arise from the incorporation of extensively heat treated egg and milk in diets of egg and milk allergic children. The first is the lessening of dietary restrictions, potentially resulting in improved quality of life for both the allergic child and the family. The ability to incorporate extensively-heated CM
(“baked” CM) liberalises the diet and also may reduce anxiety over accidental ingestion. Moreover, the benefits of introduction, in terms of reducing anxiety relating to accidental exposure, may indeed be even greater in children with past history of anaphylaxis, where severity of past reaction and length of dietary exclusion has been shown to be associated with reduced quality of life. Other benefits include the potential for altering the natural history of the disease, and accelerating acquisition of tolerance to egg and/or milk. Whilst high level evidence from well-designed randomised controlled trials is currently lacking, evidence from quasi-controlled trials is suggestive of a positive effect of regular ingestion of baked allergen on time to resolution of egg6 and CM allergy. It has also been suggested that regular ingestion of modified allergens may reduce the risk of severe or even fatal allergic reaction with inadvertent exposures, however this remains hopeful conjecture at this stage.

WHAT ARE THE POTENTIAL RISKS ASSOCIATED WITH PERMISSIVE ALLERGEN EXPOSURE IN CHILDREN WITH IgE-MEDIATED ALLERGY TO EGG AND CM?

Although dietary incorporation of extensively-head modified allergens are likely to become standard practice over the next few years for children with egg and cow’s milk allergy, there have been a few concerning reports of the development of eosinophilic oesophagitis (EoE) following SOTI to egg6 and milk. It is possible that EoE could also be precipitated by incorporation of extensively heat-treated egg and milk. Therefore careful follow-up of such patients is advised, with particular attention to any emerging symptoms suggestive of EoE.

There is a relatively small but real risk of anaphylaxis on initial challenge to extensively heated egg and CM in those children with IgE-mediated allergy, who have been strictly avoiding all forms of the allergen in their diet, where there is no history of tolerance to modified protein on accidental exposure. Rates of anaphylaxis from previous studies range from 0-6% of total cohorts and up to 20% of all reactors. For this reason most experts recommend extensively heated CM and egg oral food challenges (OFC) be performed in medically supervised settings for such allergic children.

MECHANISM OF TOLERANCE TO EXTENSIVELY HEATED ALLERGENS

The mechanism by which CM allergic children may tolerate baked CM, but not other forms of CM, is likely to be related to several factors, including the protein denaturation resulting in conformational changes in the major allergenic epitopes. Tolerance to egg in its baked form may also relate to the interaction between the matrix components, such as wheat, and the egg proteins in baked cakes and goods and is unlikely to be an effect of a lower dose exposure alone.

Tolerance to heat susceptible allergens may reflect the nature of the underlying allergy, with some evidence to suggest that those who are tolerant to heated CM represent a subgroup of children who have transient, rather than persistent CM allergy. Children tolerant to baked CM are reported to have less severe reactions to follow-up whole CM challenge than those reacting to baked CM, suggesting that children with CM allergy, who tolerate the baked CM, may represent a different clinical phenotype to their baked CM-allergic counterparts. Moreover CM allergic and egg allergic children who are exposed to frequent baked allergen demonstrate immunological changes consistent with the induction of tolerance, implying a immunotherapeutic effect rather than just cohort selection.

EXTENSIVELY HEAT-TREATED COW’S MILK TOLERANCE IN IgE-MEDIATED CM ALLERGY

Allergy to CM is one of the most common food allergies in childhood and dietary avoidance can be burdensome because of the ubiquitous nature of CM in Western diets. Several groups have reported that up to 75% of CM allergic children (IgE-mediated) can tolerate extensively-heated CM, in baked products such as cakes and biscuits in serving size quantities. Furthermore, regular ingestion of baked CM products has been shown to potentially accelerate acquisition of tolerance to CM compared with a control group of children who were continuing dietary strict avoidance.

Determining which CM allergic child is likely to be tolerant to baked CM would have significant clinical utility, as outside of some UK centres, most allergists and specialist society guidelines recommend baked CM OFC for children who have been strictly avoiding all CM in their diet, in all forms, should be performed in medically supervised settings. This however places a significant burden on currently overstretched food challenges services, and stratification to determine which children are unlikely to pass baked OFC would be very helpful. Several parameters have been previously reported to be associated with a higher risk of reacting to heat modified CM during OFC, however these parameters do not always allow individual determination of risk. Previous reported predictors of reacting to baked CM include specific IgE reactivity to the heat-stable milk protein casein as well as basophil reactivity. We have recently found that CM allergic children with the combination of...
multiple IgE-mediated food allergies, asthma and who have had prior anaphylaxis to other foods, appear particularly at risk of reacting to baked CM (in press, Annals of Asthma Allergy and Immunology). Although prior anaphylaxis to CM was associated with a higher risk of reacting on baked CM OFC, 60% of children with such a prior history were tolerant at baked milk OFC. Therefore, we have suggested that a past history of CM anaphylaxis is not a contraindication to baked CM OFC.

**EXTENSIVELY HEAT-TREATED HEN’S EGG TOLERANCE IN IgE-MEDIATED EGG ALLERGY**

Egg is a very common food allergy worldwide and the most common cause of IgE-mediated food allergy in Australian infants, with a prevalence of 9%.25 Up to 70% of egg allergic children tolerate extensively heated egg in their diet at OFC, whilst still being allergic to the native protein as well and others have previously shown.12,13,18

Higher ssIgE to ovomucoid appears to be associated with a higher likelihood of being unable to tolerate extensively heated egg in muffin or cake on OFC.26,27 Ovomucoid SPT wheal size of >11 mm has been shown to be associated with more severe generalised allergic reaction on baked muffin OFC.28 Although the British Society of Allergy and Clinical Immunology (BSACI) support a home baked egg challenge protocol for selected egg allergic children without a prior history of asthma,29 most other authors and experts recommend that these challenges still take place in a supervised setting, in view of the potential for anaphylaxis.14,28

**SPECIFIED ORAL TOLERANCE INDUCTION (SOTI)**

SOTI has become of intense interest to patients, the media and the food industry. Much like traditional subcutaneous and sublingual immunotherapy for aeroallergen and venom allergy, immunotherapy for food allergy is based upon administration of gradually increased doses of allergen, most commonly via the oral route, with up-dosing and maintenances phases. Clinical trials to date have tended to be small, with egg, milk and peanut as the most frequently examined allergens. Randomised Controlled Trials (RCT) have shown SOTI with egg, cow’s milk and peanut can induce desensitisation in a significant proportion of allergic children.30 However, most SOTI studies to date report high rates of adverse events during SOTI, causing withdrawals of up to 10-20% of patients, with up to one quarter of subjects suffering frequent adverse reactions.

The current state of SOTI for food allergens has recently been comprehensively reviewed by several leading food allergy experts.31,32 A recent meta-analysis concluded that SOTI cannot currently be recommended for routine clinical practice and that larger, better designed RCTs are required.33 However, pressure is such that SOTI is currently being conducted outside of research studies and trials as a clinical therapy in some centres,34 despite urging from most experts to not rush into suboptimal practices without a high level evidence base.35-37 Despite this, in most regions access to SOTI for food allergic patients remains currently limited to participation in clinical trials.

**DESENSITISATION OR LONG TERM TOLERANCE WITH SOTI?**

Most primary outcomes in SOTI studies have assessed desensitisation rather than sustained long term tolerance and only a few more recent studies have conducted long term follow up. Those studies with follow up have generally shown disappointingly low rates of sustained tolerance, with the vast majority achieving only a temporary state of desensitisation, which is rapidly lost without regular ongoing exposure to the allergen.38-40 Most recently reported is data from an open cohort study now in its 5th year, demonstrating long term tolerance, after being off daily therapy for one month, in 12 of 39 peanut allergic subjects enrolled in open peanut SOTI pilot, 24 of whom reached desensitisation.41 The Immune Tolerance Network IMPACT trial is evaluating long-term tolerance among children with peanut allergy in a randomised 3-year peanut OIT trial to further address this issue.42

**MECHANISM OF INDUCTION OF TOLERANCE - SOTI**

Markers of desensitisation and tolerance in SOTI have been reported by a number of groups. In general, SOTI is associated with an early increase in allergen specific IgE levels with low dose allergen and then a plateau and later decrease, to less than pre-treatment levels. In association, allergen specific IgG4 is often noted to increase over the course of successful immunotherapy treatment.43 Reduction in epitope diversity with long term SOTI has been reported and reduction in reactivity in the basophil activation test (BAT) also appears to correlate with successful induction of desensitisation.45

Induction of allergen specific T-regulatory cell populations may be important for desensitisation,46 although some studies have failed to find significant Treg induction as a marker for successful tolerance.47 Predictors of sustained unresponsiveness in long term peanut SOTI are reported...
to be baseline peanut-specific IgE/total IgE ratio, whereas in the same study, reduction in Ara h2-specific IgE level at end of therapy best correlated with sustained tolerance to peanut. Peanut-specific IgG4 was not a useful predictor of tolerance in this cohort.41

**EGG SOTI**

Several published studies have examined the efficacy and safety of desensitising children to egg.39,40 The largest and most recent of these examined the effect of daily egg immunotherapy on 55 egg allergic and sensitised children.40 The study was randomised and blinded during the initial up dosing and maintenance phase (10 months) until the time of the first oral challenge. Children undergoing active treatment then continued receiving daily egg in an unblinded fashion until 22 months, were rechallenged and then had a further challenge following 2 months without daily egg. Overall 30 of 40 children were considered to have been desensitised, however, only 11 of these children had sustained tolerance following 2 months without the daily egg therapy.

**MILK SOTI**

A 2012 meta-analysis47 of 5 milk SOTI trials considered to be of suitable quality (out of a total of 16 RCT) concluded that although the quality of evidence was low, desensitisation was achieved in the majority of individuals treated, but long term tolerance had not been shown, and there was a high rate of adverse effects and lack of standardised protocols.

**PEANUT SOTI**

A 2012 Cochrane review of SOTI for peanut allergy48 found only one small peanut SOTI trial (n=28)43 which satisfied inclusion criteria. SOTI appeared effective for desensitisation, but was associated with a high rate of adverse effects and the authors recommended larger RCT before SOTI for peanut allergy could be recommended. A 2014 meta-analysis included 3 studies (SLIT and OIT with a total 86 participants) and concluded that a significant effect on desensitisation was found but that further larger studies were required.35 Subsequently the STOP II trial was published, which reported less side effects in a RCT of 99 peanut allergic children, as determined for inclusion into the study by DBFC, using a lower dose and longer up-dosing regimen. Desensitisation was confirmed for 62% (24 of 39 participants). The maximum daily peanut maintenance in this study was 800 mg, and the cumulative total food challenge dose was 1.4 g peanut protein. This is a low total cumulative dose, and may have skewed the true desensitisation rate, with changes in threshold rather than actual desensitisation, in some children. Moreover, long term tolerance was not assessed, as the authors state based upon previous studies, it was unlikely to be successful.49

**MULTIPLE FOODS SOTI**

A recent phase one safety and feasibility trial in which food allergy children undertook daily multiple food SOTI (n=25) reported feasibility with multiple foods, with longer up-dosing phases required, but similar overall safety compared with those children undergoing peanut SOTI alone (n=15).50

**MODIFIED PEANUT AND SOTI**

We have recently shown that boiled peanut may offer a potential alternative to roasted or raw peanut SOTI. Boiling of peanuts has been shown to reduce the 2S globulins and Arah2/6 and removes significant amounts of protein from the peanuts into the boiling water.51 We identified a small number of children who were either de novo boiled peanut tolerant, or tolerant following exposed to regular increasing amounts of boiled peanut. These patients had significant reactivity to Arah2, which may explain why they tolerate boiled peanut with little side effects. (In press, JACI). Based upon these preliminary results, a RCT of boiled peanut for children with peanut allergy is currently in progress in Australia and the UK (BOPI-ACTRN-12614000265673).

Other approaches to modification of peanut protein have been reported to offer potential benefits over traditional SOTI. Polyphenolic phytochemicals, which have high affinity to bind proteins and form soluble and insoluble complexes, have been shown to reduce in vitro IgE binding and reduce basophil degranulation.52

**SOTI WITH ADJUVANTS**

The potential to improve efficacy and safety and to decrease side effects in SOTI has prompted trials involving combination adjuvant and oral immunotherapy protocols. These include:

**Biologics and SOTI**

There are now a number of reports of the use of anti-IgE co-administered with SOTI in an attempt to accelerate up-dosing schedule53 and/or reduce side effects and improve efficacy.54 A phase one CM study reported relatively few side effects and allowed desensitisation in the majority of participants.55 Similar results were reported from phase one study using omalizumab with multiple food SOTI.56 Mechanistic studies have demonstrated deletion of allergen-specific T cells following high dose cow’s milk SOTI and omalizumab therapy, suggesting a plausible rationale
for the long term tolerance, which is hoped to be obtained using this combination therapy. Overall, the use of anti-IgE in combination with SOTI requires confirmation in larger cohorts within well conducted RCTs. In addition, other biologic agents such as interferon-gamma have been trialled as adjunct therapy in SOTI.

Probiotics and SOTI
The potential of probiotics co-administered with oral food allergens has been investigated in the murine model, where efficacy and protection against experimentally induced food anaphylaxis has been demonstrated. A current clinical trial is underway in a Melbourne, Australia based RCT (P-POIT study, ACTRN12608000594325) examining the effectiveness of probiotics and peanut SOTI (P-POIT) in children with peanut allergy.

Other adjuvants
A multitude of other adjuvants have been considered for potential use for food allergy immunotherapy. These include chitosan, CpG motifs and parasites and are detailed in a recent review of emerging therapies for food allergy.

OTHER IMMUNOTHERAPY ROUTES
The finding that patients undergoing birch sublingual immunotherapy (SLIT) were noted to have improvement in their oral allergy symptoms led to the possibility that SLIT might be an effective route for the treatment of other food allergies, where the primary sensitising agent is not an aeroallergen. Small clinical trials utilising food-based SLIT have now shown some efficacy by increasing threshold eliciting doses for allergic reactions to CM, hazelnut, peanut and kiwi fruit. Most recently, the trans-epithelial route has been reported in a trial of milk allergic children, however no change was noted in the subsequent eliciting dose between control and intervention groups. A phase 2 trial of epicutaneous peanut immunotherapy within the CoFAR network is currently underway (ClinicalTrials.gov identifier: NCT01904604).

OTHER THERAPIES
Currently under investigation are Chinese herbal preparations, which have been examined at the Mount Sinai Centre in New York and collaborating institutions for some years. There is encouraging animal data where the herbal mixture FAHF-2 was demonstrated to completely block experimentally induced peanut anaphylaxis in sensitised mice. Phase 2 human studies are now underway.

Allergen-specific T-cell epitopes are targets for a novel potential therapy in food allergy which seeks to induce immunomodulation and oral tolerance by administration of short T-cell epitope peptides, which can target allergen specific T cells without binding IgE. Animal models have demonstrated efficacy, and desensitisation has been trialled in human subjects with insect and cat allergy but not, as yet, in food allergy. Promisingly, candidate T-cell epitopes for peanut have been identified and research is on-going.

THE FUTURE
With the increasing worldwide prevalence of food allergy comes a renewed impetus for targeting disease modification rather than simply allergen avoidance. Standardisation of study protocols will assist in the harmonisation and pooling of clinical trial data from RCT of immunotherapy and will provide higher quality evidence for the induction of tolerance in food allergy. Liberalisation of allergen avoidance diets can not only improve the quality of life of children with food allergy, but may hasten or alter tolerance acquisition. Whereas SOTI is currently recommended in the research setting only, over the next few decades it is likely that immunotherapy for food allergy will become a standard clinical tool using adjuvant and modified allergens, which will provide sustained tolerance rather than transient desensitisation for the majority of food allergy individuals.

DECLARATION OF CONFLICT OF INTEREST
The author declares no conflict of interest.

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