



New developments in immunotherapies for food allergy

Food allergy affects around 10% of the population. As the prevalence of food allergy continues to increase, disproportionately in children, new therapies for food allergy are being investigated. While there are no approved treatments for food allergy, immunotherapy facilitates significant desensitization and protection from accidental exposure. Nevertheless, current immunotherapies do not entirely nor permanently eliminate sensitivity to the food allergen. Since the rates of sustained unresponsiveness are significantly lower than desensitization, future therapies that enhance the rates of long-term tolerance in patients will catalyze progress in this field over the next 5–10 years.

Keywords: food allergy • immunological tolerance • immunotherapy • OIT • omalizumab • oral immunotherapy • SLIT • sublingual immunotherapy

Food allergy is defined as an adverse immune reaction to a specific food or foods that can result in serious and life-threatening hypersensitivity responses. It is estimated that it affects anywhere between 1 and 10% of the population. In addition to the deleterious health effects, the economic impact of food allergy in the USA is staggering – estimated to be US\$24.8 billion annually [1,2]. Unlike asthma, the majority of the costs of living with food allergy are not direct medical costs but costs to the family by way of lost productivity, cost of special foods and additional care-giving responsibilities [2].

Of concern, the prevalence of food allergy has increased from around 3% of children in the late 1990s to over 5% today [3] and more than a third (38.7%) of these children experience reactions that would be classified as severe anaphylactic symptoms including shortness of breath and decreased blood pressure [4]. In addition to increasing prevalence, the cost of treatment is rising also [5], despite there being very limited treatment options at this time. Currently there are no approved prevention strategies, treatments or cures for food allergy. While several key

questions remain unanswered in food allergy (How do we predict which patients are at highest risk for anaphylaxis? Why do only a small number of allergens account for the majority of food allergies? Why are some food allergies more likely to be outgrown [6]? Why is it that people with food allergy generally have antigen-specific IgE (sIgE), while not all people with sIgE get food allergy?), a key area of progress has been in developing immunotherapy approaches for treatment.

Treatments for food allergy – including food avoidance, immunotherapy and non-specific allergen therapy – are the major subject of ongoing clinical trials and basic science research. The traditional clinical recommendation of strict food avoidance, although effective, can leave children in fear of accidental exposure and at nutritional risk [2,7]. Several novel therapies undergoing clinical trials do appear to facilitate ingestion and protect patients from accidental exposures, and the field seems primed for the discovery and development of robust, targeted long-lasting immunotherapies.

One key aspect of discussing the recent developments in immunotherapy approaches

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for food allergy relates to terminology, with recent clinical trials advancing our understanding of short-term desensitization versus long-term tolerance. Desensitization is often used in immunotherapy to foods and refers to a temporary and reversible state that is defined by clinical findings and the child's ability to ingest more food while on treatment compared with pretreatment. Nonresponder tolerance or sustained unresponsiveness has also been observed in subsets of patients on food immunotherapy. In sustained unresponsiveness, patients are able to ingest the food without adverse reaction ~4 weeks after cessation of therapy. However, it has yet to be determined if this type of tolerance persists without continued ingestion. Immunological tolerance, in contrast, is the permanent nonresponsiveness to food antigens. Immunological tolerance in food allergy is best described when patients 'outgrow' their allergy, as often occurs during childhood with foods such as egg and milk, while is rare for foods such as shellfish and peanut. These patients are able to eat as much or as little food whenever they see fit (*ad lib* feeding). So far, based on oral immunotherapy studies for peanut, egg and milk, it is still unclear whether food allergy immunotherapy drives only desensitization, catalyzes the development of natural tolerance or induces an entirely separate type of tolerance. Several studies have attempted to define if the permanent establishment of immunological tolerance can be achieved by immunotherapy [8–12] and 'sustained unresponsiveness' has been used as the readout.

This review seeks to address the most recent developments in understanding how immunotherapy strategies for food allergy can provide therapeutic benefit and to discuss aspects of whether desensitization or immunological tolerance can be achieved.

Recent clinical advances

Given the rise in prevalence of food allergies and the significant impact that it has on patients and their families, there has been tremendous effort to make clinical advances through primary prevention, allergen avoidance, nonspecific and specific medical therapies. The main food-specific immunotherapies for IgE-mediated food allergy that are being evaluated for clinical practice include oral immunotherapy (OIT), sublingual immunotherapy (SLIT), epicutaneous immunotherapy and recombinant protein therapy.

Oral immunotherapy

Although still very much under investigation, OIT is the best-studied strategy for food allergy treatment. Despite variations in the dosing, duration and formulation, among others. Between trial protocols, OIT for food allergy generally involves three phases: initial dose

escalation, buildup and maintenance. Subsequently, an oral food challenge (OFC) is used to determine the level of clinical reactivity and if it has been diminished (Figure 1).

Success of OIT has varied in the generally small clinical studies studying its effectiveness, with desensitization ranging between 46 and 90% of patients, and the rates are similar for each food type: 62–89% (peanut), 64–90% (milk) and 57–90% (egg) [9,12–16]. While each of these controlled OIT studies had similarities, they can be differentiated from one another based on their patient population, duration of therapy, maintenance dosing and targeted food. Critically, most of the initial studies focused predominantly on clinical desensitization rather than sustained unresponsiveness as the clinical outcome. Two follow-up studies on patients several years after completing milk OIT trials have revealed that only a small subset of desensitized patients actually went on to develop immunological tolerance and were able to ingest milk *ad lib* without treatment after study completion [17,18].

Interestingly, animal models have helped understand the likely mechanisms responsible for OIT. One example is the generally accepted concept that low doses of the antigen induce regulatory T cells (Tregs) while high doses induce lymphocyte anergy and deletion [19–21]. The potential importance of the Treg compartment, antigen dosage and formulation to the process of food allergy resolution has received attention using murine models [22]. Additionally, using an oral-delivery based murine model of OIT, Leonard *et al.* were able to demonstrate the mice established desensitization but failed to establish tolerance to egg [23].

In the clinic, three recent studies of OIT have focused on peanut allergy, and employed double-blinded placebo-controlled food challenges to demonstrate desensitization to peanut flour [9,24–25]. Peanut and tree nut allergies are rarely outgrown, and thus achieving sustained unresponsiveness through OIT may be more difficult. Looking deeper into these studies highlights the beneficial outcomes but also some of the limitations within the studies, as well as key differences between them.

Anagnostou *et al.* released the results of the STOP II trial early in 2014, which was an unmasked, randomized controlled crossover trial of peanut OIT conducted in the UK. The primary outcome of this study was essentially desensitization and did not examine if patients achieved sustained unresponsiveness or long-lived tolerance. To evaluate quality of life a questionnaire (Food Allergy Quality of Life – Parent Form) evaluated three main areas – emotional impact, food anxiety and social/dietary limitation – using a six point scale. In total, 39 of 49 patients that were randomized

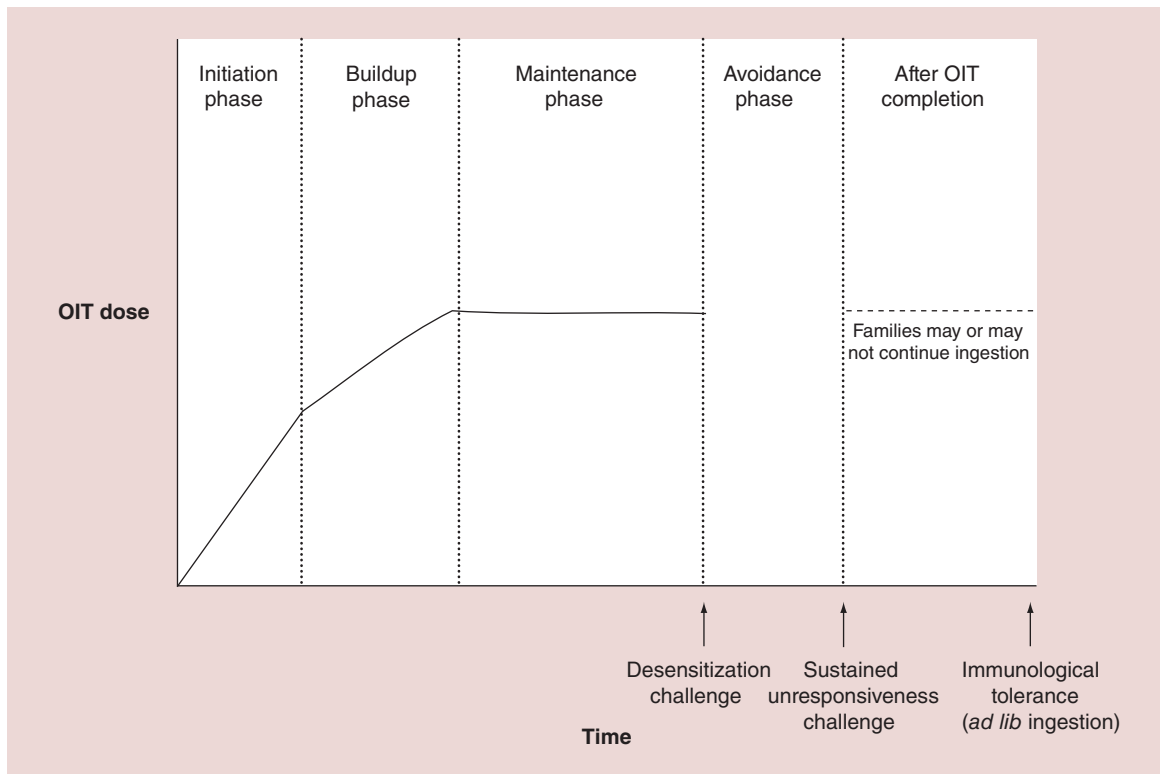


Figure 1. Schematic representation of the phases of oral immunotherapy and associated oral food challenges. Desensitization challenge is performed after the completion of the maintenance phase of therapy. Sustained unresponsiveness challenge is performed ~4 weeks after cessation of therapy. Immunological tolerance is assessed much later after the completion of the OIT protocol and is found if the child/patient can eat the food *ad lib*. OIT: Oral immunotherapy.

into the active intervention group completed 6 months of OIT with a 800 mg maintenance dose of peanut protein. Additionally, 62% (24 of 39 patients) passed an OFC – having no reaction to peanut after a cumulative dose of 1400 mg peanut protein. Moreover, 54% of the control group also passed their OFC after crossing over to OIT while still taking their maintenance doses in Phase 2 of the study [24]. This study clearly demonstrated a strong successful desensitization and improvements to quality of life after OIT and achieved this over a relatively short time frame of treatment.

Similarly, in 43 patients (23 undergoing OIT and 20 abstaining from peanut), Syed *et al.* report 87% desensitization after a somewhat longer (24 months) build-up dosing to 4 g of peanut protein. However, after 3 months of removing peanut dosing from their diet, only 35% of patients remained desensitized and this dropped further to only 13% after 6 months. Interestingly however, the clinically unresponsive patients – examined at 3 months after withdrawal – did show enhanced migratory and suppressive function of their antigen-induced Tregs and decreased methylation of the *FOXP3* gene [25], suggesting that some epigenetic enhancement of antigen-induced Tregs may be

occurring during the generation of sustained immune tolerance.

Vickery *et al.* had a lengthier period of therapy with 24 of 39 patients able to complete a mean of 3.98 years of OIT. Immediately after stopping OIT, 93% patients successfully passed an OFC with 5 g of peanut protein. Despite this excellent rate of desensitization, only 12 of 24 (50%) patients passed a repeat OFC 1 month after stopping therapy [9]. Unlike the previous study that suggested changes in Tregs, this work found no difference in peanut-specific Tregs; however, patients with sustained unresponsiveness had smaller skin prick test (SPT) responses at OFC than desensitized patients.

Finally, according to a recent double blind study, peanut OIT co-administered with the probiotic *Lactobacillus rhamnosus* may increase rates of desensitization and sustained unresponsiveness [12]. From 62 patients (31 undergoing probiotic *Lactobacillus rhamnosus* and 31 receiving maltodextrin as placebo), Tang *et al.* report that the active group achieved 90 desensitization and 82% sustained unresponsiveness, which was evaluated in patients after 2–5 weeks off of study treatment. In contrast, in the control group, only 7.1 were desensitized and 3.6% achieved sustained unresponsiveness.

Notably, the authors did not have enough patients to include a peanut OIT group without probiotics. Therefore, it is unclear what the rate of sustained unresponsiveness would have been with OIT alone (and probiotics alone) and whether the synergy of probiotic and peanut OIT enhances sustained unresponsiveness above peanut OIT alone.

In addition to peanut OIT, several nonrandomized intervention studies and randomized controlled trials have shown that OIT for cow's milk allergy can also effectively induce full desensitization in 62 and partial desensitization in 25% of patients [26,27]. Accidental exposure to milk in schools is more common than for peanut and egg, and in addition, it may be harder for children to avoid milk than it is to avoid peanuts. Two studies have performed long-term follow-up studies for cow's milk OIT [17,18]. Meglio *et al.* followed up on 21 children who underwent milk OIT, with 85% becoming desensitized. Follow-up after 4 years and 8 months revealed that 70% of the children totally or partially tolerated cow's milk, with cow's milk being present in their diet [18]. As seen after peanut OIT, the patients that exhibited this sustained unresponsiveness had decreased SPT responses. Interestingly, in this milk OIT follow-up study, tolerant children also showed a significant reduction of serum casein and α -lactalbumin-specific IgE (cow's milk antigens) while the patients who required continued OIT treatment to remain desensitized did not [18]. Follow-up of two other cow's milk OIT studies that had similar desensitization outcomes initially, revealed that 50% of patients have sustained unresponsiveness after a median of 4.5 and 3.2 years, respectively [28,29]. Consequently, compared with peanut OIT, milk OIT appears to have a higher capacity for generating tolerance and/or sustained unresponsiveness. One potential explanation for the difference in tolerance induction is that OIT treatment enhances the likelihood or rate of natural tolerance, and that the differences in success between milk and peanut studies reflect the differences in natural outgrowth between these two allergens [30,31].

There have also been attempts to perform OIT to egg and, like peanut and milk OIT, these report high rates of desensitization that are sustained only in a subset of patients [8,32–33]. Burks *et al.* examined sustained unresponsiveness to egg as far as 14 months following the discontinuation egg OIT and while 75% of children were desensitized after a treatment window of 22 months, the subset of patients that went on to develop sustained unresponsiveness was only 28 at 2 months and 25% at 14 months after OIT completion [8], seeming to again support the concept that OIT induced a tolerance response in a unique subset

of patients with perhaps a predilection for developing tolerance naturally. Mechanistically, the sustained unresponsiveness 2 months after OIT completion correlated with higher egg-specific IgG4 levels and lower SPT responses but not with egg-specific IgE levels and basophil activation.

OIT for multiple foods

Remarkably, while much of the progress to date has focused on developing therapies and treatment regimens for single-specific food allergies, nearly 30.4% of food allergic children actually have multiple food allergies and this percentage may be growing [4]. Perhaps due to the high risks for an adverse reaction seen with single-food OIT and the effectiveness of rush desensitization, OIT trials in which multiple foods are delivered have begun to include co-treatment with omalizumab, an anti-IgE monoclonal antibody that prevents IgE-driven mast cell activation. Begin *et al.* first demonstrated the safety of OIT to multiple allergens without omalizumab. Comparing 15 subjects who were monoallergic to peanut and underwent single-food OIT allergy with 25 patients who had additional food allergies, this initial study demonstrated that the rate of adverse reactions during multiple-food OIT were no higher than single-food OIT [34]. In a recent Phase I clinical trial for OIT to multiple foods, Begin *et al.* employed rush desensitization with up to five food allergens under cover of omalizumab [35]. The results of this study suggest that omalizumab in conjunction with multiple-food OIT could facilitate more rapid desensitization to multiple foods. Further investigation is needed to further determine safety and impact on sustained unresponsiveness. So far, in food allergy, OIT to multiple foods concurrently has been reported with a rush desensitization protocol with omalizumab, and additional randomized controlled trials with a placebo arm and a single-food OIT arm are necessary in order to determine if multiple-food OIT improves sustained clinical unresponsiveness.

Sublingual immunotherapy

Similar to OIT but delivered under the tongue rather than swallowed, cumulative results from SLIT clinical trials for food allergy have shown that SLIT patients have fewer systemic reactions than OIT studies [29,36–37], in stark contrast, subcutaneous immunotherapy studies have reported higher rates of IgE-mediated systemic adverse reactions in the early phases of therapy [38].

SLIT has been studied for cow's milk, peanut, kiwi, hazelnut and peach. In a small study comparing milk SLIT and OIT, Keet *et al.* found that SLIT resulted in 10% desensitization (1 of 10 subjects), which was significantly less than the 80% desensitization in

OIT-treated group. However, after 6 weeks of avoidance, only the desensitized patient in the SLIT group had developed sustained tolerance to milk [29]. More recently, in patients with peanut allergy, Fleischer *et al.* studied SLIT in 20 patients and found that 70% of subjects (and 15% of controls) became desensitized to peanut after 44 weeks of therapy [39]. Despite the potential for fewer side events, SLIT has shown modest clinical effect when compared with OIT and very little is known about its ability to induce long-term tolerance. Overall, OIT has been more effective, but with more severe adverse events [10]. A larger controlled trial would help clarify: what doses and duration of SLIT are necessary and whether it can be as effective as OIT at desensitizing children with fewer adverse events.

Novel/experimental approaches

Other food-allergen-specific therapies are being developed in an effort to reduce adverse events during desensitization and improve rates of sustained unresponsiveness. Epicutaneous immunotherapy, or skin patch based delivery of antigen, is a novel delivery strategy that has been shown to be efficacious for aeroallergies [40]. It has begun to gain attention as a food allergy therapy both in the USA and in Europe. Initial safety trials have confirmed the safety and tolerability of the patch for milk allergy [41]. After a Phase Ib (NCT01170286) trial confirmed safety with limited local cutaneous adverse events for epicutaneous peanut immunotherapy, a Phase II trial (NCT01197053, ARACHILD) was undertaken to test the efficacy of the epicutaneous patch in peanut allergic patients. While epicutaneous delivery of antigen is less invasive, concerns might be drawn from murine models of food allergy that show antigen delivery via the skin actually promotes IgE sensitization [42,43]. To answer whether these phenomena also occur in humans, further investigation of the patch-based delivery system is needed but, from the mechanistic research from various fields, the skin is certainly a site of antigen sensitization.

Peptide and engineered recombinant protein immunotherapy involve the delivery of targeted epitopes in order to maximize signals to the immune system via T-cell binding and minimize IgE-mediated activation of mast cells. A Phase I clinical trial involving the rectal delivery of Ara h1, h2 and h3 with heat-killed *Escherichia coli* as an adjuvant ended prematurely because it resulted in acute adverse reactions in 50% of peanut allergic subjects [44]. Despite this, current investigations include modifying the peanut (Ara h1, h2 and h3) and cow's milk antigens (α -lactalbumin and β -lactoglobulin) by changing internal IgE-binding sites or purifying out tolerogenic epitopes. Further research is needed to investigate how these peptides

can be modified to take on more tolerogenic properties while reducing adverse events during administration.

Efforts that reduce adverse reactions to therapy

Omalizumab (anti-IgE) has been studied as a single therapy for IgE-mediated peanut allergy. While omalizumab alone does seem to reduce reactions during OFCs, the Phase II trial was stopped prematurely due to two anaphylactic reactions early in the study [45–47]. Subjects often cite oral and abdominal side effects as reasons for withdrawing from OIT studies. Due to the adverse reaction rate, trials including co-treatment with omalizumab have been undertaken and there is now some evidence that omalizumab as adjunctive therapy to OIT may be a more effective protocol. This is based on studies including an uncontrolled Phase I trial of omalizumab with OIT in which eleven patients with milk allergy across two institutions were enrolled. Remarkably, nine subjects were rush desensitized to 1000 mg of milk powder in the first day and able to tolerate greater than 240 ml of milk in maintenance [48]. In a subsequent – similarly small – uncontrolled study with 13 high-risk peanut allergic patients, omalizumab pre-treatment allowed all patients to reach a dose of 500 mg peanut flour within the first day. While patients in this peanut study experienced higher grade reactions than in the milk study, desensitization in 100% of patients to 500 mg of peanut flour in 1 day has not been reported in slower peanut OIT protocols [49].

A novel development in anti-IgE therapy, called designed ankyrin repeat proteins (DARPs), may also hold some promise as an adjunct to OIT. DARPs are small, highly stable nonimmunoglobulin proteins that mimic the binding site of the high affinity IgE receptor (Fc ϵ RI) and in turn prevent the binding of IgE to Fc ϵ RI and the subsequent signaling cascade. Eggel *et al.* recently showed *in vitro* that DARPs designed against IgE-Fc ϵ RI complexes accelerate dissociation of IgE from Fc ϵ RI and remove already attached IgE more effectively than omalizumab. In addition, *in vivo* studies in murine models of anaphylaxis demonstrate that DARPs disrupt the IgE-Fc ϵ RI complexes and inhibit responses even more effectively than omalizumab [50].

Development of eosinophilic esophagitis after oral immunotherapy

Some investigators have provided case reports describing children undergoing OIT who subsequently develop eosinophilic esophagitis (EoE); however, the causative relationship between OIT and EoE has yet to be determined [51–53]. Many patients (up to 81% depending on the study) experienced adverse events while on OIT [24]. Upper respiratory tract symptoms and abdominal

pain/nausea during the dose escalation phase of OIT protocols are commonly experienced by patients and gastrointestinal symptoms are one of the most frequent reasons for discontinuing therapy. In peanut OIT subjects, abdominal pain/nausea can account for nearly 30% of patient reported reactions [51,54]. In a milk OIT study, 12 of 25 patients in the treatment group reported nausea and vomiting symptoms and only 3 of 20 subjects in the elimination diet group [55]. Biopsy-proven EoE has been reported [52,56], but the true incidence of EoE while on OIT may be higher than reported as patients often discontinue therapy due to symptoms and do not undergo endoscopy and biopsy for definitive diagnosis. Further, upon reintroduction of the offending food, symptoms can often include abdominal pain, nausea and oral pruritus, which are common to both IgE-mediated food allergy and EoE [57]. Additionally, some children show an increased sensitivity to food allergens after OIT, and there are examples of children with significant symptoms after OIT requiring more frequent epinephrine use [17,26]. As described previously, the reversibility of desensitization has been observed as early as 1 week after completing egg OIT and continues to be true 3–5 years later in milk OIT studies [17,29,58]. Knowing that subjects often rebound out of their desensitized states rapidly after allergen avoidance, the risk/benefit profile of OIT becomes much more complex. One possibility is that the repeated exposures and symptomatic activation within the upper gastrointestinal and/or respiratory system actually induces local inflammatory events within the esophagus, but this remains to be established. Clinically, it seems increasingly clear though that it is important to monitor children for EoE in the following years after completing therapy [52].

Mechanisms of desensitization & immunological tolerance

The outcomes from the clinical trials for food allergy therapies suggest that desensitization and long-term tolerance are very different states of immune modulation. To date, we have made only modest strides in our understanding of the mechanisms of natural and induced oral tolerance versus desensitization. Speaking generally, during desensitization, OIT appears to modulate the immune system by suppressing mast cell and basophil effector functions while, later on, some patients achieve sustained unresponsiveness or immunological tolerance with changes in the immune response that include the maintenance of Treg populations and suppressive cytokines like IL-10, a reduction of allergen-specific T cells, an increased antigen-specific IgG4 levels as well as potentially a more sustained suppression of the mast cell and basophil compartment.

Cellular changes during desensitization

The protection against reactivity offered by OIT at the desensitization phase is not associated with any significant reduction in food-specific IgE and yet SPT reactivity does decrease shortly after starting OIT, and might even decrease more significantly in those patients that go on to develop sustained unresponsiveness [8,29,39,59]. Through the early initiation doses, OIT seems to modify the sensitivity of mast cells and/or basophils, cells that have been shown to be necessary in murine anaphylactic food allergy models [60,61]. Interestingly, the deletion of mast cells and phagocytes, but not mast cells and basophils, confers the best protection against the anaphylactic response in peanut-sensitized mice [60].

The way in which these cells have changed their ability to release soluble mediators and drive anaphylaxis has not been fully characterized. Histamine, tryptase, chymase, heparin, cytokines and lipid mediators produced by mast cells and basophils are all important to consider when characterizing mast cell/basophil suppression in desensitized patients. However, significant evidence points toward an important role for histamine, which contributes to both cutaneous responses and anaphylaxis in IgE-mediated acute allergy syndromes. We, and others, have shown that anaphylactic responses are mediated via two of the histamine receptors, H1R and H2R [62,63]. Mast cell and basophils are also modulated by other components of the immune system, and so with the appropriate duration of immunotherapy it seems likely that Tregs, allergen-specific T cells, sIgE and sIgG4 also exert downstream effects on mast cell/basophils responsiveness.

Select immune changes associated with sustained unresponsiveness

Not all people with high sIgE levels are allergic to that food, and therefore food-specific IgE tests have a low specificity for clinical diagnosis [64]. Moreover, reductions in serum sIgE are not always seen in patients that have sustained unresponsiveness after OIT and instead, there has been interest in IgG4. For example, Burks *et al.* demonstrate significant changes to SPTs, basophil activation, sIgG4 and sIgE but not total IgE in egg OIT-treated children that are desensitized at 22 months. Those differences in sIgE did not persist after completion of therapy even at 24 months – just 2 months later [8].

In contrast, the maintenance of FoxP3⁺ regulatory T cells appears to correlate with the development of oral tolerance. Given that Tregs can suppress IgE-mediated mast cell degranulation after antigen exposure [65,66], maintenance of the Treg pool may be a more reliable marker for sustained unresponsiveness than sIgE. Syed *et al.* showed that OIT through dendritic cells results in epigenetic changes at the *FOXP3*

locus. The end result is that immune tolerant patients show increases in FoxP3 expression, migration of antigen-induced Tregs to the mucosal site and suppressive function of antigen-induced Tregs [25]. Moreover, IPEX patients (X-linked neonatal diabetes mellitus, enteropathy and endocrinopathy syndrome) who have mutations in *FOXP3* get severe food allergy [67]. Comparably, Treg deficient mice and Foxp3-mutant mice fail to establish oral tolerance and are more susceptible to allergic disease [67,68]. Our lab has shown that transferring Tregs in to mice with food allergy protects the mice from mast cell-dependent anaphylaxis [66].

IgG4 antibody levels increase shortly after starting OIT and continue to increase significantly in patients with sustained unresponsiveness [8,59,69–70]. More recently, the induction of antigen-specific IgG antibodies during OIT has been shown to play a protective role during IgE-mediated responses including anaphylaxis [71]. Antigen-specific IgG4, more so than the other IgG subclasses, is thought of as a sponge that soaks up antigen before it has an opportunity to activate the effector cells like mast cells and basophils. This new study adds to that knowledge by suggesting that the suppressive action IgG4 is due to its signaling through FcγRIIb receptor and the subsequent inhibition of FcεRI-mediated activation [71]. The types of immune cells induced by OIT – maintenance of Tregs and skewing away from allergen-specific T_H2 cells – could contribute to the sustained increase in IgG4 (and the less reliable decrease in sIgE) that we see in tolerant patients.

What remains to be discovered is how effector cells, which are present systemically such as in the mucosa and skin, contribute to the generation of immunological tolerance over desensitization. Additionally, it is still not known how natural tolerance and induced tolerance differ immunologically. Future food-allergen-specific immunotherapies should aim to generate natural tolerance in patients as closely as possible while balancing the risks of the treatment.

Conclusion & future perspective

Immunotherapy for food allergy is at an exciting time – we are able to draw from a number of clinical trials of immunotherapy to better understand the key concepts of desensitization versus tolerance, and future trials are being considered and performed to better inform on the mechanisms of responses. In combination with mechanistic research from animal models and identification of novel pathways, the future of immunotherapy for food allergy looks bright.

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Executive summary

Recent clinical advances

- The prevalence and economic impact of food allergy is increasing.
- Immunotherapies for food allergy commonly induce desensitization, but not tolerance.
- Oral immunotherapy (OIT), the best-studied approach, induces desensitization effectively.
- Epicutaneous immunotherapy and peptide immunotherapy are examples of novel approaches currently being investigated.
- Omalizumab and designed ankyrin repeat proteins (anti-IgE therapies) show promise as adjuncts to OIT.
- Rates of eosinophilic esophagitis in children after undergoing OIT are being monitored.

Mechanisms of desensitization and tolerance

- Desensitization via OIT involves the suppression of mast cell and basophil function.
- Sustained unresponsiveness correlates with:
 - Maintenance of Tregs and a suppressive cytokine environment;
 - Reduction of allergen-specific T cells;
 - Increased antigen-specific IgG4.
- Antigen-specific IgE levels are an imperfect predictor of food reactivity.
- Further research is needed to determine how effector cells contribute to immunological tolerance over desensitization.

Conclusion

- Impactful advances have been made in the field of food allergy immunotherapy recently.
- OIT trials have guided mechanistic research in animal models and vice versa.
- It is not known how desensitization and immunological tolerance differ mechanistically.
- Identifying the factors that promote immunological tolerance over desensitization will improve the effectiveness of food allergy immunotherapies.

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