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Invited review article

Active treatment for food allergy

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Abbreviations:
OIT, oral immunotherapy; SLIT, sublingual immunotherapy; EPIT, epicutaneous immunotherapy; SCIT, subcutaneous immunotherapy; CM, cow's milk; OFC, oral food challenge; FAHF, food allergy herbal formula; RCT, randomized controlled trial; IT, immunotherapy; EoE, eosinophilic esophagitis

ABSTRACT

Food allergy has grown in rapidly in prevalence, currently affecting 5% of adults and 8% of children. Management strategy is currently limited to 1) food avoidance and 2) carrying and using rescue intramuscular epinephrine/adrenaline and oral antihistamines in the case of accidental ingestion; there is no FDA approved treatment. Recently, oral, sublingual and epicutaneous immunotherapy have been developed as active treatment of food allergy, though none have completed phase 3 study. Efficacy and safety studies of immunotherapy have been variable, though there is clearly signal that immunotherapy will be a viable option to desensitize patients. The use of bacterial adjuvants, anti-IgE monoclonal antibodies, and Chinese herbal formulations either alone or in addition to immunotherapy may hold promise as future options for active treatment. Active prevention of food allergy through early introduction of potentially offending foods in high-risk infants will be an important means to slow the rising incidence of sensitization.

Background

An allergic reaction to food is defined as an IgE mediated reaction to ingestion of a specific food. Symptoms of food allergy may include abdominal pain, vomiting, urticaria and anaphylaxis. The prevalence of food allergy has risen considerably in recent years, now estimated to be 5% in adults and 8% in children, with some regional variability.[1–5] Estimates of growth in incidence of food allergy range from 18% from 1997 to 2007, to a doubling over the past decade.[3,6] With the incidence of food allergy rising so quickly, there has been an intensification of research efforts directed toward finding a treatment and eventually a cure.

Management of food allergy currently consists of strict and careful food avoidance, while keeping emergency treatment available at all times.[7] If an allergenic food is ingested, this is treated with intramuscular epinephrine/adrenaline or oral antihistamines (or occasionally systemic corticosteroids), depending on the age of the patient, severity of the reaction and the amount ingested. Without a pharmacologic option for active treatment, families are forced to remain ever-vigilant, closely monitoring food labels, taking caution with food at social gatherings and carrying an epinephrine/adrenaline auto-injector at all times. The stressful psychological effect that food allergy has on patients and their families is quite apparent, and quality of life is diminished.[8] Families have reason to be stressed, as accidental ingestion occurs frequently[9]: one study reported that up to 75% of patients with peanut allergy will accidentally consume peanuts.[10] Furthermore, treatment of accidental ingestions with an epinephrine/adrenaline auto-injector is anxiety provoking and perceived by patients and families as challenging.[11] The anxiety surrounding the potential for a severe reaction any time food is consumed significantly diminishes quality of life for patients and their families.

Food allergy is currently treated by a combination of specific food avoidance, provision of emergency treatment, and monitoring. Specifically, patients are told to specifically avoid the food to which they're allergic, which can be challenging given the

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large number of ingredients in commonly consumed foods. If a patient is accidentally exposed to an offending food, they are treated emergently with intramuscular epinephrine/adrenaline and oral antihistamines, as described above. Monitoring involves frequent food-specific IgE and skin prick testing. An oral food challenge (OFC) may be attempted as a patient develops a pattern that may be consistent with tolerance. The OFC represents the gold standard for diagnosis of food allergy, since some patients will spontaneously develop tolerance to previously offending foods over time.

Although food allergy is a commonly encountered problem, active treatment toward desensitization has been limited to the research setting. In this paper, we define desensitization as an increase in threshold reactivity for a particular subject, and sustained tolerance as retention of that increased reactivity threshold for months to years without further treatment. Subcutaneous immunotherapy (SCIT) for peanut allergy was studied in the 1990s, though in this trial, the rate of severe reactions was unacceptably high.[12] Since then, oral, sublingual, and epicutaneous immunotherapy, have been described in a number of trials, as have recombinant vaccines, immunobiologics, bacterial adjuvants and herbal therapeutics (Table 1).

The goal associated with food immunotherapy remains controversial. While some feel the goal should be to induce desensitization and sustained unresponsiveness, others feel that a small amount of tolerance – allowing a patient to tolerate an accidental bite of an offending food, for example – is clinically and emotionally significant. In this review, we highlight trials that look at both types of endpoints. Food allergy is a common problem resulting in significant physical, emotional and psychiatric morbidity and mortality; it is therefore necessary to find a safe, efficacious management strategy.

Allergen specific therapies

Subcutaneous immunotherapy

Subcutaneous immunotherapy was employed in 1992 for desensitization of peanut allergic subjects.[13] Patients in this study completed an initial rush schedule followed by maintenance dosing. After promising initial results, the study was terminated early due to a fatal reaction. The fatality occurred following a formulation error in the pharmacy, wherein a placebo-treated patient received a maintenance dose of immunotherapy.

Since subcutaneous immunotherapy had been so successful in treating aeroallergy, the technique was reattempted for active treatment of food allergy, this time in an adult study.[12] Unfortunately, a very high rate of systemic reaction occurred: 23% of patients during rush buildup and 39% during maintenance doing.

Recombinant proteins for use in SCIT, thought to potentially enhance safety, was reported by Zuidmeer-Jongejan *et al.* in 2012.[14] From this group, we can expect to see development of novel proteins representing the active allergens in peach and fish, which may be better tolerated than the unaltered food. Human studies in this arena have not been reported to date.

Table 1
Change in biomarkers after active treatment with immunotherapy.

Biomarker	Change after immunotherapy
Skin prick reactivity	↓
Allergen specific IgE	↓ (after initial increase)
Allergen specific IGG4	↑
Basophil activation	↓

Oral immunotherapy

Oral immunotherapy (OIT) involves exposing patients to escalating doses of the offending food with the goal of inducing desensitization or sustained unresponsiveness (Tables 1–4). OIT has primarily been attempted in the research setting and is not FDA approved. A typical OIT protocol involves an entry challenge to establish clinical reactivity, followed by escalating doses of the offending food until a pre-specified maintenance dose is achieved for a pre-specified amount of time. If this maintenance dose is successfully achieved, the patient is said to be *desensitized*. After that, the maintenance dose may be discontinued for a pre-specified amount of time and the patient rechallenged with the offending food. If the subject does not react, he or she has been said to have achieved *sustained tolerance*.

Side effects of OIT continue to be elucidated, and most commonly include abdominal pain and oral pruritus (75%, Table 3). More severe side effects such as eosinophilic esophagitis (2.7%) and severe reactions requiring intramuscular epinephrine/adrenaline (25% of patients, Table 3) are not uncommon.[15–18]

The mechanism of action of OIT is postulated to involve modulation of the immune response (Table 1). Specifically, a decline in specific IgE and concomitant increase in protective IgG4, as well as induction of basophil activation anergy and increased regulatory T-cells have been shown.[19–21] Mast cells, basophils and neutrophils are all involved in the anaphylactic response, and are likely modified by OIT.[22] B cell populations associated with food allergy have been described, along with changes in their IgG4 repertoire induced by OIT.[23]

Oral immunotherapy for food allergy has been reported as early as 1998, though more recent trials have exhibited higher degrees of control and randomization; these will be reviewed below.[24]

Peanut OIT

While advances in OIT continue rapidly, there is still no FDA-approved treatment available, and a recent Cochrane review reports uncertainty associated with this approach.[25] In a 2009 landmark peanut OIT randomized controlled trial (RCT), children with peanut allergy underwent an OIT protocol including initial day escalation, buildup and maintenance phases, and then OFC.[26] This systematic approach is typical of most RCTs for food allergy. Twenty-nine subjects completed the protocol, 27 of whom successfully ingested 3900 mg of peanut protein (equivalent to about 16 peanuts) following treatment. Mechanistic data reported included diminished skin prick test reactivity, peanut specific IgE, and basophil activation in the treatment group, with peanut-specific IgG4 significantly increasing.

In 2011, peanut OIT was further explored in another RCT, examining 28 subjects aged 1–16 years.[27] All 16 children in the treatment arm tolerated 5000 mg of peanut protein (roughly 20 peanuts) after OIT. Mechanistic data was of similar pattern to that

Table 2
Tolerance and sustained unresponsiveness induced by oral immunotherapy (OIT), sublingual immunotherapy (SLIT), and epicutaneous immunotherapy (EPIT).

Type of IT	Tolerance	Sustained unresponsiveness
OIT	>60%	10–50%
SLIT	10% (70% show modest level of tolerance)	Minimal
EPIT	Modestly induced in 28–50%	None demonstrated to date

Tolerance is defined by being able to tolerate the food in a typical diet. Sustained unresponsiveness is defined as being able to tolerate the food in a typical diet after immunotherapy has been terminated.