

Oral and sublingual immunotherapy for food allergy

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Summary

Objective: Food allergies continue to be an increasingly common disorder, however, no treatment strategies are currently approved for the routine management of individuals with food allergies. Encouraging results from early open-label studies have sparked great interest in oral and sublingual immunotherapy, and thus several randomized controlled trials have recently been conducted to establish the safety and efficacy of these treatment strategies. The aim of this review is to examine the recent studies for peanut, milk and egg allergies.

Data Sources: Open-label and randomized control trials are discussed.

Study Selections: Studies focusing on peanut, milk and egg allergies are included.

Results: Current evidence indicates that desensitization is possible for the majority of subjects who undergo oral immunotherapy. Clinical improvement has been associated with favorable immunologic changes, including smaller skin prick test wheal sizes and increased allergen-specific IgG₄ levels. Adverse reactions are common, however, and thus safety concerns remain. Sublingual immunotherapy thus far has not proven to be as effective as oral immunotherapy.

Conclusion: Oral and sublingual immunotherapy are promising treatments for food allergy. Optimization and standardization of protocols, along with additional assessments of safety are still needed. (*Asian Pac J Allergy Immunol* 2013;31:198-209)

Key words: Food, allergy, anaphylaxis, treatment, tolerance

Introduction

Food allergy continues to affect an increasing number of people^{1,2} and for many, the allergy is a persistent issue throughout adolescence and adulthood.³⁻⁵ Current management entails avoidance of food allergens and preparation for treating allergic reactions since effective therapies are not yet available. While vigilance with food allergen avoidance, accurate reading of ingredient labels and care with cross-contamination can minimize the risk of allergic reactions, inadvertent exposures leading to potentially life-threatening reactions still occurs.⁶⁻⁸ This creates a significant burden not only on the affected individual, but also for their family and friends. Thus, efforts to develop safe and effective therapies are necessary for food allergy.

Immunotherapy entails the incremental dosing of allergenic protein administered to selected patients in physician-monitored, controlled clinical settings over a period of time. The goal is to reach a target maintenance dose that is continued for a period of time with the goal to achieve immunologic non-response. The mechanism underlying this clinical and immunologic non-response is believed to be through down-regulation of Th2 responses.⁹ This immunologic non-response can be transient, requiring continued allergen exposure to maintain the effect (desensitization), or sustained regardless of whether the patient continues regular or sporadic consumption of the allergen (tolerance).

The concept of immunotherapy (IT) is not new; the earliest attempt with subcutaneous IT for food allergies resulted in unacceptably high rates of serious side effects,¹⁰ and therefore this method was deemed unsuitable for routine treatment of food allergies. More recently, oral administration has been explored since allergen exposure via the oral mucosa has been found to be tolerogenic.⁹ Sublingual administration, while only allowing smaller doses to be given, takes advantage of the tolerogenic antigen-presenting cells in the oral mucosa and may allow food proteins to bypass gastric digestion.¹¹ Early studies have demonstrated promising results, prompting additional studies using refined protocols (randomized, placebo-controlled trial design) which give the highest

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Submitted date: 18/4/2013



quality of evidence for safety and efficacy. Here we review recent advances in immunotherapy for food allergy to peanut, milk and egg.

Efficacy of OIT and SLIT: clinical and immunologic outcomes

Peanut oral immunotherapy

A recent Cochrane report identified 16 studies examining the effects of oral immunotherapy (OIT) for peanut allergy.¹² Of these, 15 were excluded for reasons including lack of a control group, case reports, use of the a form of IT other than OIT, and lack of information regarding the outcome measures of desensitization or tolerance. Only one randomized controlled trial has been published to date for peanut oral immunotherapy.¹³ In this study, 28 children ages 1-16 years were enrolled. Nineteen received active treatment and 9 receive placebo. Subjects underwent dose escalation for 44 weeks and were maintained at the target dose of 4000mg peanut protein for an average of 4 weeks. Sixteen (84%) of the subjects who received active treatment were able to reach the target dose and complete the protocol; all of these passed the 5 gram oral food challenge (OFC) at the end of the study. While no baseline OFC was performed, the median cumulative dose tolerated by the placebo group was significantly lower at 280mg. Associated immunologic changes included decreased skin prick test (SPT) wheals, increased allergen-specific IgG₄ (sIgG₄), and decreased IL-5 and IL-13 production by peripheral blood mononuclear cells (PBMCs) by the end of the study. Allergen-specific IgE (sIgE) was increased after 2 months of OIT, but was not different from baseline by the end of the study.

Of the 4 studies reporting clinical outcomes,¹⁴⁻¹⁷ the protocols aimed for target doses ranging from 300-800mg daily for 6-8 months. A majority (61-100%) of enrolled subjects ages 1-16 years were able to reach the target maintenance dose in each of these studies. Of those who were able to reach the target dose,^{14-15,17} 49/52 (94%) tolerated the end of study OFC assessing for desensitization. One study performed the final OFC 2 weeks off OIT.¹⁶ In this study, 11 out of the 14 (79%) who reached the 500mg maintenance dose were able to tolerate a higher dose whereas 3 subjects tolerated less than the maintenance dose, suggesting that tolerance may be achievable in some patients, but not others. Although most studies excluded those with a history of anaphylaxis, Anagnostou et al.¹⁷ chose to include children with a history of anaphylaxis to peanut in

their open label study, however, a sub-analysis of outcomes within this group was not reported.

Changes in immunologic parameters were measured in several of these studies. Smaller SPT wheal diameters were seen as a result of OIT,^{13-14,16-17} but Blumchen et al.¹⁶ noted that this decrease was not seen after OIT was discontinued for 2 weeks. More variable changes were seen with sIgE. Some studies observed increases in sIgE early in OIT,^{13,17} but end of treatment results showed little or no change in most studies.^{13,16-17} When measured, increases in sIgG₄ were observed.^{13-14,16} Using peptide microarray, the decrease in sIgE and increase in sIgG₄ levels were associated with changes in epitope binding patterns, indicating that OIT induces shifts in the antibody repertoire.¹⁸ Decreases in Th2 cytokine production by PBMCs were reported as well.^{13-14,16}

Milk oral immunotherapy

A Cochrane review was also conducted for milk OIT.¹⁹ Of 157 records reviewed, only 16 records, which reflected 5 clinical trials, were included as these were the only randomized controlled trials.²⁰⁻²⁴ These studies all included pediatric patients with IgE-mediated cow's milk allergy. Four studies required baseline OFCs as an entry criterium.^{20,22-24} In 4 studies, a target dose equivalent to a full serving of milk (150-200mL milk) was maintained for 4-12 months.^{20-21,23-24} The success rate for desensitization ranged from 36%-90%, with the lowest success rate reported for the one study which exclusively selected for those with a history of anaphylaxis to milk and significantly elevated IgE level to milk (sIgE > 85 kU_A/L).²⁰ If this study is excluded, then the rate of successful desensitization was 67-90%, comparable to the outcomes of the peanut OIT studies. One other study chose to include milk allergic children with any history of reaction and reported that within the subset of children with a history of anaphylaxis, the success rate for OIT was 80%.²¹ Reasons for differences between the OIT success rates in children with history of anaphylaxis between these 2 studies are unclear and may be due to differences in sIgE levels as only 2 of the children in the study by Salmivesi et al.²¹ who completed the protocol had sIgE > 70 IU/L whereas all children in the study by Longo et al.²⁰ had sIgE > 85 kU_A/L.

One study chose a significantly lower target dose of 15mL daily for 13 weeks.²² Even at this low dose, all subjects receiving active treatment had significant increases in threshold at the end of study OFC (median 5100mg vs 40mg in the placebo

group). Two subjects completed the 8 gram OFC with no reaction, suggesting that low OIT doses can induce immune modulation as well. Thus, the Cochrane review concluded that these studies support a significant effect of milk OIT regardless of age or history of anaphylaxis.¹⁹

Similar to the peanut OIT studies, decreases in sIgE were seen in some,^{20,23} but not others.^{22,24} Significantly increased sIgG₄ levels were reported in 2 studies that examined this parameter.^{22,24}

Egg oral immunotherapy

Fewer studies have examined the efficacy of OIT for egg allergy. To date, the largest multi-center double-blind, randomized control trial of egg immunotherapy enrolled 55 children ages 5-11 years old.²⁵ Forty subjects received active treatment and 15 subjects received placebo. Baseline OFC was not performed in this study. Subjects underwent an initial day dose escalation, build-up to a target dose of 2000mg of egg white powder over a maximum of 10 months, and then continued at this maintenance dose daily for at least 2 months prior to the first OFC (10 month OFC, 5 grams). The study was unblinded at this point and actively treated subjects continued the maintenance dose through the second OFC (22 month OFC, 10 grams). Subjects who passed the 22 month OFC then discontinued OIT for 4-6 weeks and returned for a final OFC to determine tolerance (24 month OFC, 10 grams). At the 10 month OFC, 22 actively treated subjects passed the 5 gram challenge (55% success rate). Fourteen completed the OFC with no symptoms, while 8 had mild-moderate symptoms that self-resolved without treatment. By the 22 month challenge, an increased number of subjects passed a 10 gram OFC (n=30, 67%, ITT). Of these, 29 subjects discontinued OIT and returned for the tolerance OFC at 24 months. Eleven subjects demonstrated sustained unresponsiveness despite interruption of therapy, indicating that tolerance could be achieved in a subset of the treated group (27.5%, ITT). These children continued to incorporate egg into their diets without adverse events at follow-up at 30 months.

Two earlier studies also examined the efficacy of OIT in desensitizing and inducing tolerance in young egg allergic children. In a proof of concept study, Buchanan et al.²⁶ enrolled 7 children (median age 44.7 months, range 14-84 months) who underwent an OIT protocol that involved an inpatient modified rush phase, build-up phase at home to a target dose of 300mg of powdered egg white, and a maintenance phase during which the

target dose was taken daily for the duration of the study (24 months). Four children (57%) passed the 10gram OFC at the end of treatment. Of these, 2 developed tolerance since they passed another 10 gram OFC 3 months after OIT was discontinued. Vickery et al.²⁷ used a different approach where dosing of OIT was individualized based on egg white sIgE. As long as the sIgE remained >2kU_A/L, subjects underwent reassessments with OFC every 4 months and up-dosing of the OIT to a maximum daily dose of 3600mg powdered egg white. Whenever the sIgE was <2kU_A/L, subjects discontinued OIT and underwent a 10 gram OFC. Repeat OFC off therapy was offered to those who passed the desensitization OFC. Eight children (median age 5 yrs, range 3-13 yrs) were enrolled and 6 completed the OIT protocol over 18-50 months (median 33mo). The maintenance dose reached ranged from 300-3600mg (median 2400 mg). All 6 subjects who completed treatment passed both the desensitization and tolerance OFCs. All these subjects successfully incorporated egg into their diets.

Immunologic parameters showed decreased sIgE in the one study where the protocol and timing of OFCs were individualized based on sIgE levels.²⁷ No changes in sIgE were observed in the other studies.²⁵⁻²⁶ In contrast, increases in sIgG₄ were reported for all these studies, again consistent with peanut and milk OIT studies.²⁵⁻²⁷ Basophil activation was investigated in one study and was reported to be decreased after OIT.²⁵

Peanut sublingual immunotherapy

An alternative route for immunotherapy that has been explored is sublingual administration. This has been shown to be an effective strategy with aeroallergens in the treatment of allergic asthma and rhinitis, and has demonstrated a favorable safety profile.^{28,29} Two randomized controlled trials of sublingual immunotherapy (SLIT) for peanut have been published to date. Kim et al.³⁰ enrolled 18 subjects (median 5.2 yrs, range 1-11 yrs) in a 12 month study using a target dose of 200mcg of peanut protein. Eleven subjects received active treatment, 7 received placebo. At 12 months, OFC was performed. The active group consumed a median cumulative dose of 1710mg peanut protein as compared to 85 mg for the placebo group. Immunologic changes seen at 12 months included smaller SPT wheal diameters, decreased sIgE, increased sIgG₄, decreased IL-5 production by PBMCs stimulated with crude peanut extract (CPE) *in vitro*, and decreased basophil responsiveness

when stimulated with CPE. No significant differences were seen in the percentage of T regulatory cells or PBMC production of other cytokines.

In the recent multi-center, double-blind, placebo-controlled trial of peanut SLIT, 40 subjects were enrolled.³¹ This study included older subjects, median age was 15 years (range 12.2-36.8 years). Subjects underwent a baseline 2 gram OFC prior to starting the SLIT protocol. Maintenance doses ranged from 165-1386 mcg peanut protein. A 5 gram OFC was performed at week 44. Responders were defined by the ability to tolerate 5grams or having a 10 fold increase in threshold dose as compared to the baseline OFC. Fourteen subjects receiving active treatment were considered responders (70%). None of the subjects were able to complete the 5 gram OFC without symptoms, indicating a modest desensitization effect. Of note, 8 responders tolerated <500 mg at OFC. In the placebo group, 3 were considered responders. Two placebo-treated subjects developed spontaneous tolerance to peanut over the course of the trial, emphasizing the importance of having placebo controls in these trials. Although more subjects in the active group were considered to be responders as compared to the placebo group, the median successfully consumed dose (SCD) was no different from the placebo group. The responders continued on SLIT and had a repeat OFC at 68 weeks. At this point, a subset of responders had an increased SCD, indicating that prolonged treatment may increase efficacy. However, for 2 subjects, the SCD decreased at the 68 week OFC despite continuing on SLIT for an additional 24 weeks. Seventeen placebo treated subjects were crossed-over to receive high-dose SLIT and subsequently underwent an OFC at week 44. Within this group, 88% reached the target maintenance dose of 3696 mg. Forty-four percent were responders, however, 4 had a SCD <500mg. Among all treated subjects, clinical improvements were not correlated with decreases in sIgE. Active treatment did result in increased sIgG₄ levels, however, there was no difference between responders and non-responders. In general, SLIT responders did have smaller SPT wheal diameters than non-responders at week 68.

Milk sublingual immunotherapy

SLIT for milk allergies was first reported in an open-label study of 8 children (median 8.5 yrs, range 6-17 yrs).³² These children underwent a baseline OFC prior to starting on 6 months of SLIT with a target dose of 1ml/day cow's milk. Six

subjects completed the protocol. An increase in mean eliciting dose was seen after treatment as compared to pre-treatment (143 mL vs 39 mL, no p-value provided), and 3 subjects had no symptoms at the final OFC. A more recent study also examined SLIT for milk allergy.³³ In this open label study, 10 subjects underwent a SLIT protocol which entailed escalation to a target dose of 7mg daily. After 12 weeks on maintenance, a 7-fold increase in threshold dose at OFC was seen. This increased to a median increase of 40-fold by 60 weeks. Only 1 subject was considered to be fully desensitized, having passed the 8gram OFC. This subject had no reactions following repeat challenges 1 and 6 weeks off therapy and was considered to be tolerant. Consistent with OIT studies, an initial increase in sIgE was observed during dose escalation. By the end of treatment, significant decreases were seen for sIgG₄ and skin prick test reactivity. Basophil activation was evaluated in this study and no changes were observed after SLIT treatment.

Overall efficacy of immunotherapy for food allergies

In summary, many studies have demonstrated that desensitization using OIT can be achieved for the majority of children for peanut, milk and egg allergies. However, variations in immunotherapy protocols make direct comparisons and evaluation of true efficacy difficult. A wide range of doses has been used for peanut OIT (300-4000mg peanut protein), milk OIT (15-200mL cow's milk), egg OIT (300-3600mg egg white powder), peanut SLIT (2000-3969mcg), and milk SLIT (7-33mg). These studies have primarily been in children and include a range of reaction severity history. From these studies, we have learned that several factors may influence the outcomes of OIT. For example, the success rates for studies that included primarily younger children tended to be higher than those which included a wider or older age range, suggesting that immune modulation with IT may be more effective when started earlier in life.^{23,30} Two studies which included children with a history of anaphylaxis had lower success rates for desensitization as compared to studies that excluded those with a history of anaphylaxis.^{16,20} Several studies suggest that longer durations of treatment with higher maintenance doses may be more effective.^{25,27,31,34} Since standard immunotherapy for aeroallergens and insect venoms is generally continued for 3 or more years, it would be reasonable to believe that food allergen immunotherapy would require comparable durations of treatment.



Table 1. Summary of studies reviewed

	Subjects	History of anaphylaxis	Baseline OFC	Trial design	Target maintenance dose and duration	Clinical outcome	Drop outs	Adverse events (AEs)
Peanut OIT study								
Varshney, 2011	28 children, 1-16yrs	excluded	no	RCT – 2:1 Active:placebo	Target maintenance dose = 4000 mg Duration of OIT = 48wks	16 reached the target maintenance dose and passed 5gm OFC	3	AEs: 47% had AEs on initial escalation (2 epinephrine) build-up phase 1.2% of 407 doses had AEs (0 epinephrine)
Jones, 2009	39 children, 1-16 yrs	excluded	no	Open label	Target maintenance dose = 300 mg Duration = 8 mo	29 reached the target maintenance dose; 93% passed 3.9gm OFC	10	93% had AEs
Clark, 2009	4 children, 9-13 yrs	included	yes	Open label	Target maintenance dose = 800 mg Duration at target =6 weeks	All subjects reached the target maintenance dose and passed 2.38gm OFC	0	No epinephrine needed for AEs
Blumchen, 2010	23 children, 3-14 yrs	included	yes	Open label	Target maintenance dose = 500 mg Duration at target = 8 weeks	14 reached the target maintenance dose; At the final OFC 2 wks off OIT, 11 tolerated higher dose than maintenance	8	AEs: 7.9% OIT rush doses 2.6% OIT doses No epinephrine needed for AEs
Anagnostou, 2011	22 children, 4-18 yrs	included	yes	Open label	Target maintenance dose = 800 mg Duration = 30 weeks	19 reached the target maintenance dose; 95% passed the 6 wk 2.6 gram OFC and 30 wk 6.6 gram OFC	1	No epinephrine needed for AEs

Table 1. (Continue)

	Subjects	History of anaphylaxis	Baseline OFC	Trial design	Target maintenance dose and duration	Clinical outcome	Drop outs	Adverse events (AEs)
Peanut SLIT study								
Kim, 2011	18 children, 1-11 yrs	excluded	no	RCT – 11 active, 7 placebo	Target maintenance dose = 2000 mcg Duration = 12 months of SLIT; 6 of these months on target dose	Active group consumed median of 1,710mg PN vs 85mg for placebo group	0	AEs: 11.5% PN doses, 8.6% placebo doses No epinephrine needed for AEs
Fleischer, 2013	40 subjects, 12-37 yrs	excluded	yes	RCT, 1:1	Target maintenance dose = 165-1386 mcg Target maintenance dose for cross-over group = 3696 mcg Duration = 44 wks	70% responders in active group vs 15% in placebo Cross-over group 44% responders **2 placebo pts had spontaneous tolerance to PN during course of trial	10	AEs: 0.6% placebo doses 40.1% of 5,825 SLIT doses had AEs (1 treated with epinephrine) Cross-over group (higher target dose): 33% doses had AEs
Milk OIT study								
Longo, 2008	60 children, 5-17 yrs	included	yes	RCT, 1:1 Co-intervention: antihistamine	Target maintenance dose = 150 mL Duration = 1 year at target dose	Active group: 36% desensitized, 54% could take limited amounts of milk	3	All subjects in the active group had AEs Active group: 4 were treated with epinephrine during the rush phase; 18 had respiratory symptoms during the rush phase that required treatment with inhaled epinephrine 1 subject was treated with epinephrine for an AE during home dosing

Table 1. (Continue)

	Subjects	History of anaphylaxis	Baseline OFC	Trial design	Target maintenance dose and duration	Clinical outcome	Drop outs	Adverse events (AEs)
Martorell, 2011	60 children, 24-36 months	excluded	yes	RCT, 1:1	Target maintenance dose = 200 mL Duration = 1 year at target dose	90% desensitized	2	80% subjects on active treatment had AEs 2 subjects required treatment with epinephrine during the study
Pajno, 2010	30 children, 4-13 yrs	excluded	yes	RCT, 1:1	Target dose = 200 mL Duration = 18 weeks	67% desensitized, 6.7% was partially desensitized	3	80% of active group had AEs, 2 subjects required treatment with epinephrine
Salmivesi, 2012	28 children, 6-14 yrs	included	no	RCT, 2:1 active:placebo	Target dose = 200 mL Duration = 162 (+14 days) days	89% of active group desensitized Placebo group later offered open label OIT - 100% desensitized Subset with history of anaphylaxis: 80% desensitized	4	100% of active group had AEs
Skripak, 2008	20 children, 6-17 yrs	excluded	yes	RCT – 13 active, 7 placebo	Target dose = 15 mL (500 mg) Duration = 13 weeks at target dose	Active group had significant increase in threshold at OFC (median 5100mg vs 40mg in placebo)	1	100% of active group had AEs; 4 AEs required treatment with epinephrine (2 during build-up, 2 during home dosing)
Milk SLIT study								
De Boissieu, 2006	8 children, 6-17 yrs	unknown	yes	Open label	Target dose = 1 mL Duration = 6 months	Mean eliciting dose increased from 39 mL (range 4-106 mL) at baseline to 143 mL (44->200 mL) at the end of the study 3 subjects passed the 200mL OFC at the end of the study	1	unknown

Table 1. (Continue)

	Subjects	History of anaphylaxis	Baseline OFC	Trial design	Target maintenance dose and duration	Clinical outcome	Drop outs	Adverse events (AEs)
Keet, 2011	30 children, 6-15yrs	excluded	yes	All subjects began with 4+ weeks of open label SLIT Then randomized (1:1:1) to high or low dose OIT or SLIT	Target maintenance doses = High dose OIT (2 gm) Low dose OIT (1gm) SLIT 7 mg Duration = 60 weeks	Full desensitization: 60% of low dose OIT group, 80% of high dose OIT group, 10% of SLIT group Tolerance: 30% of low dose OIT group, 50% of high dose OIT group, 10% of SLIT group	2	AEs: 29% SLIT doses, 23% OIT doses Epinephrine required to treat 6 AEs
Egg OIT								
Burks, 2012	55 children, 5-11 yrs	excluded	no	RCT – 40 active, 15 placebo	Target dose 2000mg Duration – 22 months	75% desensitized at 22 months 28% tolerant (passed OFC 4-6 weeks off OIT)	8	78% subjects receiving active OIT had AEs
Buchanan, 2007	7 children, 1-16 yrs	excluded	no	Open label	Target maintenance dose = 300 mg Duration = 24 months	57% passed 10 gm OFC after 24 months OIT 28.6% tolerant (passed OFC 3 months off OIT)	0	100% had AEs during modified rush No epinephrine needed for AEs
Vickery, 2010	8 children, 3-13 yrs	excluded	no	Open label	Target maintenance dose determined based on sIgE levels Duration = ranged 18-50 months	75% tolerant (passed OFC 1 month off OIT)	2	5 of 6 subjects had AEs on initial escalation No AEs during maintenance dosing No epinephrine needed for AEs

Regarding the route of administration of immunotherapy, OIT has been more effective than SLIT for peanut allergy, likely due to the higher target doses achievable with the oral route.^{13-17,30-31,35} A retrospective comparison of 2 previously published protocols of peanut OIT¹⁷ and peanut SLIT³⁰ demonstrates not only increased efficacy of OIT, but also greater immunologic changes.³⁵ At the 12 month OFC, OIT subjects were 3 times more likely to pass OFC than SLIT subjects (89% OIT subjects passed a 5 gram OFC vs 30% SLIT subjects passed a 2.5 gram OFC). While OIT led to higher median sIgE at 12 months, greater increases in sIgG₄ were seen at 12 and 24 months and significant decreases in basophil activation were observed at 12 months. In the study which directly compared OIT and SLIT for milk allergy, OIT treated subjects had greater fold increases in the threshold dose at OFC and higher rates of full desensitization and tolerance.³³ While these studies demonstrate that IT is a promising therapeutic strategy for food allergies, it is important to note that these studies did not use a uniform protocol, thus the optimal target dose and duration of treatment are not yet defined.

Another unanswered question is whether tolerance induction is achievable. Only a few studies thus far have addressed this question with OFCs performed after discontinuation of OIT.^{16,25-27,33} Most of these studies showed that 21-65% of children were not able to maintain the clinical effects of OIT when treatment was discontinued.^{16,25-26,33} This loss of effect was seen as soon as 2 weeks after peanut OIT was discontinued in one study.¹⁶ Similarly, loss of desensitization was observed in 11% after milk OIT was discontinued for 1 week and an additional 22% were reactive by 6 weeks post-therapy.³³ One small study of egg OIT reported that all children who completed the protocol and passed the desensitization OFC maintained this effect after 1 month off OIT.²⁷ Notably, this study used sIgE levels as a guide to determine duration of OIT rather than using a standard protocol for all subjects. Thus, all the children in this study had lower sIgE levels by the time desensitization challenge was performed as compared to subjects in the other studies.

Safety and tolerability of OIT and SLIT

While OIT and SLIT have shown clinical efficacy for desensitizing subjects with food allergies, safety and tolerability of treatment remains a concern. Variability in reporting of adverse events (AE)

complicates estimations of frequency, however, adverse effects were frequently reported and were experienced by the vast majority of individuals who underwent treatment. In studies where AE frequency was reported by subjects, 78-100% of subjects experienced symptoms with OIT.^{14,21-22,25-27} Although the symptoms were often localized, systemic reactions requiring epinephrine were seen not only during the escalation phase, but also in association with home doses.^{14,20,22} From the Cochrane review of milk OIT, for every 11 subjects who underwent treatment, 1 required intramuscular epinephrine for an adverse reaction.¹⁹ In some of these studies, the frequency and severity of adverse events as well as the demanding protocols led to drop-out rates as high as 25-30%.^{14,16,31} When comparing rates of adverse events between OIT and SLIT, Keet et al.³³ reported similar rates of symptoms between SLIT and OIT treated groups, although fewer SLIT reactions required treatment. Factors that have been reported to negatively impact the tolerability of IT doses include exercise, concurrent viral illness, suboptimal control of asthma, menses, and taking doses on an empty stomach.^{13,17}

At this point, the long-term outcomes of OIT and SLIT are uncertain. Desensitization may confer protection against reactions due to accidental ingestions, however, this protection can be quickly lost (within 1 week) with interruption of treatment.^{16,25-26,33} Even when a stable maintenance dose is continued, changes in threshold to induce a reaction have been observed. In the multi-center peanut SLIT trial, 2 subjects who responded to treatment could only tolerate a lower dose of peanut at the week 68 OFC as compared to the week 44 OFC.³¹ Thus, the risk for allergic reactions are still present, even for those who have responded favorably to treatment. Furthermore, cases of eosinophilic esophagitis (EoE) have been reported in subjects undergoing OIT^{34,36} and the true risk of EoE in subjects undergoing OIT are uncertain. Therefore, it is important for patients to consider the risks and benefits of therapy, and the quality of life before committing to this therapy, since avoidance of the food allergens and preparedness for anaphylaxis would still remain essential aspects of food allergy management; these decisions are likely to be different for different individuals.

Strategies to improve the safety profile while maintaining or enhancing the efficacy of immunotherapy include combination treatment with

omalizumab (anti-IgE), use of heat-denatured proteins, or alternate routes of administration. Treatment with omalizumab has been shown to reduce allergic symptoms in some children with food allergy and decrease IgE binding on the surface of mast cells, basophils and antigen-presenting cells, and thus should minimize adverse reactions when administered prior to initiation and during build-up of OIT.³⁷⁻³⁹ In a pilot study of 11 children with milk allergy, pre-treatment with omalizumab allowed 9 subjects to reach 1000mg milk powder on the first day of desensitization.³⁹ Over 16 weeks, 9 subjects were able to reach the target daily dose of 2000 mg milk. The rate of adverse events associated with OIT doses was 1.8%, suggesting that adjunctive treatment with omalizumab could allow more rapid escalation of OIT with increased safety.

Oral immunotherapy with heat-denatured proteins is an option for the majority of children with milk and egg allergy. In a longitudinal study of milk-allergic and egg-allergic children who were including baked milk or egg products in their diet, many of these children experienced accelerated tolerance induction.^{40,41} Inclusion of baked-milk products in the diets was safe, convenient and well-tolerated.

An alternate method of immunotherapy now being evaluated is the epicutaneous route. In a pilot study, 19 milk-allergic children were randomized to receive epicutaneous IT (EPIT) or placebo.⁴² After 3 months of therapy, half of the subjects in the active group had significantly increased the amount of milk tolerated during a follow-up OFC (>10-fold increase for 2 subjects and >100-fold increase for 4 subjects); no change in tolerated doses was seen in the placebo group. Treatment was well-tolerated and no child interrupted treatment due to AEs nor was epinephrine required. This early study suggests that epicutaneous administration may be another effective option for delivering IT.

Conclusions

Current evidence indicates that desensitization is possible for the majority of subjects who undergo oral immunotherapy, and clinical improvements are associated with favorable immunologic changes. However, adverse reactions are frequent and reactions requiring intramuscular epinephrine occur in a significant number of patients. In comparison, sublingual immunotherapy has not proven to be as effective as oral immunotherapy in short term protocols, although the safety profile is superior, and

the role of EPIT for treating food allergic patients remains to be established. Optimization and standardization of protocols, along with additional assessments of safety are still needed before OIT, SLIT or EPIT can be approved for the routine management of individuals with food allergies.

Conflicts of Interest

Julie Wang, MD has no conflicts of interest to declare. Hugh A Sampson, MD has received consulting fees from Allertein Therapeutics, LLC and is named on a patent for the food allergy herbal formula (FAHF-2).

Funding source

Julie Wang, MD is funded in part by a grant from the National Institutes of Health/National Institute of Allergy and Infectious Diseases; K23 AI083883. Hugh A Sampson, MD is funded in part by grants from the National Institutes of Health/National Institute of Allergy and Infectious Diseases; AI-44236 and AI-066738, and the National Center for Research Resources; RR-026134.

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