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IMMUNOTHERAPY AND IMMUNOMODULATORS (L COX, SECTION EDITOR)

Sublingual (SLIT) Versus Oral Immunotherapy (OIT) for Food Allergy

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Abstract Food allergy is a common condition for which the only currently approved treatments are avoidance of the allergenic food and the administration of emergency medications upon accidental exposure. Over the past 10 years, significant advances have been made in the field of food immunotherapy, with efforts focusing on allergen exposure via the oral mucosa. Oral immunotherapy (OIT) and sublingual immunotherapy (SLIT) are the two modalities that have been most extensively studied, and this article will review recent advances in our knowledge of the efficacy and safety of these treatments.

Keywords Immunotherapy · OIT · SLIT · Food allergy · Omalizumab

Introduction

Food allergy is a common condition that affects approximately 3–6 % of the US population [1], and its prevalence appears to have increased in industrialized countries over the past 15 years [2, 3]. For many individuals, food allergy persists into adolescence and adulthood [4–6], and despite careful food avoidance, life-threatening reactions to foods still occur [7, 8]. The only currently approved treatments for food allergy are food avoidance and the administration of emergency medications upon accidental exposure. Because of the unpredictability of these serious reactions and the lack of adequate treatment options, quality of life is significantly impaired in those with food allergy [9]. For these reasons, safe and effective therapies for this condition are highly desirable.

Immunotherapy relies on the delivery of increasing amounts of allergenic proteins over a period of time in a physician-monitored clinical setting, with the goal of developing desensitization and eventual tolerance to the protein. While the exact mechanisms underlying allergen immunotherapy are not fully understood, immunotherapy is known to induce allergen-specific regulatory T and B cells, which secrete IL-10 and suppress allergen-specific Th2 responses. This response is coupled with an initial increase in allergen-specific IgE and IgG4 levels, and decreases in mast cell, basophil, and eosinophil mediator release [10].

Over the past century, immunotherapy has been effectively used to treat various immediate hypersensitivity reactions, including asthma, allergic rhinitis, and venom hypersensitivity. In the early 1990s, the first trials examining immunotherapy for food allergy were conducted, using subcutaneous administration of peanut extract [11, 12]. These early trials demonstrated an unacceptably high level of systemic reactions [12], and thus, this form of therapy for treating food allergy was largely abandoned.

Despite these initial setbacks, research in the field of food immunotherapy has surged over the past 10 years, with efforts focusing on allergen exposure via the oral mucosa. Oral immunotherapy (OIT) and sublingual immunotherapy (SLIT) are two of the modalities that have been most extensively studied, and this article will review recent advances in our knowledge of the efficacy and safety of these treatments.

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OIT

Over the past 10 years, many studies have examined the use of OIT in milk, peanut, and egg allergy. In OIT, the food protein is delivered as a powder or mixed in a vehicle and ingested. This form of immunotherapy is thought to activate the gut mucosal dendritic cells, which subsequently modulate circulating effector cells [13]. Current OIT protocols typically involve three phases: (1) initial dose escalation (modified rush desensitization), during which six to eight doses of allergen are given in a single day; (2) buildup dosing, which occurs every 1–2 weeks under observation until a maintenance dose is reached, usually over a period of 6 to 9 months; and (3) maintenance dosing, with daily dosing for months to years. While the amount of protein ingested varies significantly between studies, doses typically start in milligrams and increase to grams during maintenance. These higher doses of allergen are thought to increase both immune modulation as well as the risk of adverse reactions.

Milk Allergy

In 1998, Patriarca et al. published the first controlled trial examining the role of OIT in treating food allergy [14]. Fourteen individuals who were allergic to milk, egg, fish, and/or apple underwent desensitization to the allergenic food. Twelve of the 14 individuals successfully completed the desensitization protocol, and all 12 were able to tolerate the food in the diet without any adverse reactions. Since this time, multiple trials [15–23] and two meta-analyses [24, 25•] have been published examining milk OIT, which will be summarized below as well as in Table 1.

Efficacy of Desensitization

Six randomized controlled trials of milk OIT have been published [16–19, 21, 23]. Three of these studies used food avoidance as the control [16, 19, 23], whereas the other three used a placebo control [17, 18, 21]. While the three studies comparing milk OIT to food avoidance were heterogeneous in terms of the maintenance dose (150–200 mL, equaling 5–6.67 g of milk protein) and the duration of maintenance therapy (6 months–1 year), they each found that approximately 90 % of individuals were able to consume either a partial or full serving of milk at the end of treatment. In contrast, in the control group, 0–23 % were able to tolerate milk at the end of the studies by Longo et al. [16] and Martorell et al. [19], while Morisset et al. found that 60 % of those randomized to food avoidance were able to consume 200 mL of cow's milk at the end of the study [23]. These studies demonstrate that while many children will naturally outgrow their milk allergy, milk OIT is more likely than avoidance to induce a state of clinical desensitization.

Similarly, three recent studies, with varying desensitization protocols and target maintenance doses (0.5–6.67 g/day), demonstrated that 67–92 % of individuals on milk OIT were able to complete the desensitization protocol and include milk in their diet at the end of treatment, compared to no children in the placebo arms [17, 18, 21]. In Skripak et al., when the placebo-treated children crossed over to active OIT, the median challenge threshold increased from 40 to 8140 mg using a maintenance dose of 500 mg [17].

These studies were recently examined in a systematic review and meta-analysis of milk OIT by Yeung et al. [25•]. The authors found that 62 % of individuals who underwent OIT were able to consume at least 200 mL of cow's milk, compared to only 8 % of controls (risk ratio (RR) 6.61; 95 % confidence interval (CI) 3.51–12.44). An additional 25 % (n= 27) of those on active treatment, compared to no patients in the control groups, were able to tolerate a partial serving of milk (10–184 mL/day) (RR 9.34; 95 % CI 2.72–32.09). While OIT for milk allergy appears to be efficacious, the authors concluded that the quality of evidence is low due to small studies with inconsistent methodology. Thus, larger, well-controlled studies with consistent methodology are needed prior to considering milk OIT for clinical use.

Long-Term Efficacy

While milk OIT appears to induce desensitization during treatment, few studies have examined either sustained unresponsiveness, in which individuals do not react to the food after avoiding it for a period of time, or its long-term efficacy and safety. Meglio et al. reported that 4 years after completing milk OIT, of the 18 children who achieved partial or full desensitization, 14 (78 %) were still able to tolerate milk, and no child had received emergency care for adverse reactions to milk [26]. Salmivesi et al. also examined the long-term efficacy of their OIT study discussed above. Approximately 3 years after completion of the initial study, the authors found that one child had stopped consuming milk because of an atopic dermatitis and asthma flare. When the family tried to reintroduce milk, the child developed anaphylaxis and avoided milk products thereafter. It was thus determined that the long-term success of this therapy was 79 % [21].

In 2013, Keet et al. [27•] described the long-term efficacy of two milk OIT studies performed at Johns Hopkins and Duke University [17, 28, 29••]. Subjects were contacted between 3 and 4 years after study completion and questioned about their milk consumption and adverse events. The authors found that 22 % of patients limited their milk consumption because of symptoms, including anaphylaxis, that 6 % only ate trace amounts of milk or baked milk, and that 16 % of children avoided milk entirely. These results were very concerning given that most of the children were tolerating large amounts of milk at study completion.

Table 1 Studies examining oral immunotherapy (OIT) for the treatment of food allergy

Study (year)	Food	Blinded	No. of subjects (age range)	Maintenance dose	Challenge dose[a]	Efficacy [*n* (%)][b]	Withdrawals [*n* (%)]	Tolerance [*n* (%)][c]
Meglio et al. (2004) [15]	Milk	No	21 (5–10)	200 mL/day	NA	15/21 (71)	3/21 (14)	NA
Longo et al. (2008) [16]	Milk	No	30 (5–17)	150 mL/day	150 mL	11/30 (36)	3/30 (10)	NA
Skripak et al. (2008) [17]	Milk	Yes	13 (6–16)	500 mg/day	8000 mg	12/13 (92)	1/13 (8)	NA
Pajno et al. (2010) [18]	Milk	Yes	15 (4–12)	200 mL/day	NA	10/15 (67)	5/15 (3)	NA
Martorell et al. (2011) [19]	Milk	No	30 (2–3)	300 mL/day	NA	27/30 (90)	1/30 (3)	NA
Alvaro et al. (2012) [55]	Milk	No	66 (5–16)	200 mL/day	NA	51/66 (77)	1/66 (2)	NA
Garcia-Ara et al. (2013) [20]	Milk	No	36 (4–13)	400 mL/day	150 mL	33/36 (92)	3/36 (8)	NA
Salmivesi et al. (2013) [21]	Milk	Yes	18 (6–14)	200 mL/day	NA	16/18 (89)	4/28 (14)	NA
Levy et al. (2014) [56]	Milk	No	280 (4–27)	240 mL/day	NA	160/260 (62)	39/260 (15)	NA
Patriarca et al. (2003) [22]	Milk	No	59 (3–55)	120 mL 2–3×/week	NA	45/54 (83)	9/59 (15)	NA
	Egg			1 egg 2–3×/week				
	Fish			160 mg 2×/week				
Morisset et al. (2007) [23]	Milk	No	27 (1–7)		200 mL	24/27 (89)		NA
	Egg		49 (1–8)		7 g	34/49 (69)		NA
Staden et al. (2007) [57]	Milk Egg	No	25 (0.6–13)	100 mL/day 1/4 egg daily	4770 mg 6200 mg	12/25 (48)	9/25 (36)	9 (36)
Egg OIT								
Buchanan et al. (2007) [30]	Egg	No	7 (1–7)	300 mg/day	8000 mg	4/7 (57)	0/7 (0)	2/4 (29)
Vickery et al. (2010) [31]	Egg	No	8 (3–13)	Variable	10,000 mg	6/8 (63)	2/8 (25)	3/3 (38)
Garcia Rodriguez et al. (2011) [32]	Egg	No	23 (5–17)	1 egg/day	NA	20/23 (87)	1/23 (4)	NA
Burks et al. (2012) [33••]	Egg	Yes	40 (5–11)	1/3 egg/day	5000 mg	30/40 (75)	6/40 (15)	11/40 (28)
Meglio et al. (2013) [34]	Egg	Yes	10 (6–14)	1 egg 3×/week	NA	8/10 (80)	1/10 (10)	NA
Peanut OIT								
Clark et al. (2009) [35]	Peanut	No	4 (9–13)	800 mg/day	2380 mg	4/4 (100)	0/4 (0)	NA
Jones et al. (2009) [36]	Peanut	No	39 (1–9)	300 mg/day	3900 mg	29/39 (74)	10/39 (26)	NA
Blumchen et al. (2010) [39]	Peanut	No	23 (3–14)	125 mg/day	4000 mg	14/23 (61)	7/23 (30)	14/23 (64)
Anagnostou et al. (2011) [42]	Peanut	No	22 (4–18)	800 mg/day	6600 mg	18/22 (81)	1/22 (5)	NA
Varshney et al. (2011) [37•]	Peanut	Yes	19 (3–10)	4000 mg/day[d]	5000 mg	16/19 (84)	3/19 (16)	NA
Anagnostou et al. (2014) [38••]	Peanut	No	99 (7–16)	800 mg/day	1400 mg	49/85 (58)	6/99 (6)	NA
Syed et al. (2014) [40]	Peanut	No	23 (5–45)	4000 mg/day	4000 mg	20/23 (87)	2/23 (9)	7/20 (3 months) 3/20 (6 months)
Wasserman et al. (2014) [41]	Peanut	No	352 (3–24)	Varied	NA	298/352 (85)	12/352 (3)	NA
OIT+omalizumab								
Nadeau et al. (2011) [45]	Milk	No	11 (7–17)	2000 mg/day	7250 mg	9/11 (82)	1/11 (9)	NA
Schneider et al. (2013) [46•]	Peanut	No	13 (8–15)	4000 mg/day[d]	8000 mg	12/13 (92)	1/13 (8)	NA

NA not assessed

[a] Defined as the DBPCFC cumulative dose of targeted food at the end of the desensitization protocol

[b] Defined as the number of subjects who successfully finished treatment and were able to include the targeted food in their diet or passed the post-treatment challenge after desensitization

[c] Defined as the number of children who passed a tolerance DBPCFC among those who started desensitization

[d] Peanut flour (50 % peanut protein)

Egg OIT

Efficacy of Desensitization

In 2007, Buchanan et al. published a proof-of-concept study for egg OIT, in which seven children underwent treatment with a goal dose of 300 mg egg protein/day [30]. Four of these children successfully consumed 8 g of egg protein plus one scrambled egg without any symptoms after OIT. The remaining three children had partial desensitization after OIT and were able to tolerate 2–14.7 g of egg protein in an open challenge. Since this study, four more trials have been published on egg OIT [31, 32, 33••, 34], which are summarized below as well as in Table 1.

In 2012, a multi-center study from the Consortium for Food Allergy Research (CoFAR) randomized 55 children to egg OIT (n=40), with a goal dose of 2000 mg egg protein/day or a placebo (n=15) [33••]. After 10 months of treatment, 22 children in the active group (55 %) passed an oral food challenge (OFC) to 5 g egg, as compared to no children in the placebo group (p<0.001). One year later, 30 children in the active group passed an OFC to 10 g egg (75 %). This study demonstrated that egg OIT is efficacious in inducing clinical desensitization compared to the placebo, and that efficacy appears to improve with longer duration of treatment.

Sustained Unresponsiveness

In the 2007 study of Buchanan et al. described above, the four children who passed the initial OFC were then instructed to avoid egg for 3–4 months, at which time they underwent another OFC. Two of these four children (29 %) successfully passed the OFC, whereas one child ingested 2 g and one child was only able to tolerate 24 mg before developing symptoms [30].

In the CoFAR trial, the 30 children who had successfully passed an OFC after egg OIT [33••] avoided egg for 4–6 weeks, at which time a repeat 10 g OFC was performed, of whom only 11 passed this challenge without symptoms (28 %). These children were then followed for another year, and they continued to eat egg without restriction. These two studies highlight the fact that sustained unresponsiveness is only attained in a minority of patients undergoing OIT. The factors that predict and promote the development of sustained unresponsiveness remain unclear and warrant further investigation.

Peanut OIT

Efficacy of Desensitization

Early efforts at food OIT were directed toward milk and egg, and the first studies on peanut were performed many years later. In 2009, two open-label studies on peanut OIT that provided evidence of desensitization were published [35, 36]. Clark et al. treated four children with confirmed peanut allergy, and all were able to tolerate 800 mg of peanut protein/day at the end of the study. Jones et al. enrolled 39 children, and 29 completed the protocol of ingesting 300 mg peanut protein/day. At the end of the study, 27 of the 29 children were able to pass a double-blind placebo-controlled food challenge (DBPCFC) to 3900 mg with only mild symptoms.

More recently, two randomized controlled trials of peanut OIT have been published. In 2011, Varshney et al. enrolled 28 children with confirmed peanut allergy and randomized them to receive peanut OIT (n=19), with a goal maintenance dose of 4000 mg peanut flour (2000 mg peanut protein)/day or placebo (n=9). All of the 16 children who completed active therapy and reached the goal maintenance dose passed a 5000-mg peanut flour OFC at the end of the study (84 %). In comparison, the children in the placebo group tolerated a median of 280 mg of peanut flour in the end of study OFC [37•].

In 2014, Anagnostou et al. published results of a randomized controlled crossover trial of peanut OIT. Ninety-nine children were enrolled and randomized to receive active OIT (n=49) at 800 mg peanut protein/day or placebo (n=50). After 6 months of maintenance, ten children had withdrawn from the active group, and 24 of the remaining 39 children (62 %) were able to tolerate a challenge of 1400 mg of peanut protein without any symptoms. Thirty-three children (84 %) were able to tolerate the daily ingestion of 800 mg of peanut protein for 26 weeks. In comparison, no child in the placebo group passed the OFC or was able to tolerate daily peanut ingestion. After the children in the placebo group crossed over to active OIT, 25 of the remaining 46 (54 %) were desensitized, and 91 % were able to tolerate 800 mg of peanut protein daily [38••]. While these two studies demonstrate that peanut OIT is modestly effective in inducing desensitization, the optimal maintenance dose and duration of therapy for achieving desensitization warrant further study.

Sustained Unresponsiveness

As with egg and milk OIT, few studies have examined whether peanut OIT induces a temporary state of desensitization or longer-term sustained unresponsiveness. In 2010, Blumchen et al. addressed this question in an open-label study of peanut OIT in 23 children. Of the 23 children enrolled, 14 completed the therapy and underwent a DBPCFC after 2 weeks of avoidance. Three children reacted at a lower dose than that which they had been ingesting daily, indicating a breakthrough in desensitization after just 2 weeks off therapy [39]. In 2014, Syed et al. reported results of an open-label study of peanut OIT with a dose of 4000 mg/day. Of 23 children undergoing active OIT, 20 (87 %) passed an OFC to

4000 mg at the end of treatment. These children were then instructed to avoid peanuts for 3 months, at which time a repeat OFC was performed. Seven of the 20 children (35 %) passed this avoidance OFC and were instructed to avoid peanut for another 3 months. At this 6-month follow-up OFC, only three children remained tolerant (13 %) [40].

Safety of OIT

Adverse reactions are very common with OIT, with similar rates reported for milk, egg, and peanut. Local symptoms such as oral itching are most common, and reactions are generally mild, requiring either no treatment or antihistamines. Abdominal pain is the most common symptom leading to withdrawal from treatment, and moderate reactions, such as rhinoconjunctivitis, wheezing, vomiting, and urticaria, occur in a small percent of all doses. However, given that doses are given daily, the risk for each patient over an extended course of treatment is substantial. For example, in a study of milk OIT in young children, 47 % of subjects developed moderate reactions over the course of treatment [19]. More severe reactions requiring treatment with epinephrine and beta-agonists are most common during dose escalation but can also occur during maintenance therapy [16–20]. Wasserman et al. reported that 95 reactions requiring epinephrine occurred during peanut OIT for 352 patients [41]. It is especially concerning that most severe reactions occur unpredictably, with a dose that has been previously tolerated, possibly triggered by co-factors such as infection, exercise, anxiety, or allergen co-exposure [20, 40, 42].

A particular obstacle to moving these treatments to clinical practice is the high percent of patients who cannot tolerate OIT. Overall, 10–20 % of subjects have dropped out of OIT trials, with rates as high as 36 % in some studies. While some participants have withdrawn due to anaphylaxis or other acute reactions, the vast majority of withdrawals are due to chronic abdominal pain. Eosinophilic esophagitis has been documented in some of these cases, and it is not clear how frequently undiagnosed disease may complicate OIT [43, 44]. Further studies directed at minimizing adverse reactions are therefore critically important to move these treatments forward.

Omalizumab and OIT

In the last 3 years, two studies examined the use omalizumab in combination with OIT. In 2011, Nadeau et al. treated 11 children with omalizumab for 9 weeks, at which time they underwent rapid desensitization (0.1 to 1000 mg) to milk. For the next 8 weeks, they increased their milk dose to a goal of 2000 mg. At week 16, omalizumab was discontinued and milk consumption was maintained at 2000 mg/day for another 8 weeks. Nine of the ten patients reached the daily maintenance dose of 2000 mg/day, and all nine children passed the DBPCFC to 7250 mg at week 24 [45]. This study suggested that OIT can be escalated more rapidly when combined with omalizumab, although adverse reactions were still relatively common.

In another study, the combination of OIT and omalizumab was examined in peanut allergy in a pilot study of 13 children [46•]. The children were treated with omalizumab for 12 weeks, at which time they underwent rapid desensitization to peanut (from 0.1 to 500 mg) over 6 h. For the next 8 weeks, they underwent weekly up-dosing to a goal of 4000 mg peanut flour (2000 mg protein) daily. Omalizumab was discontinued at week 20, and the children underwent an 8000-mg peanut flour DBPCFC at week 32. Twelve of the 13 children reached the goal dose, and one patient withdrew because of persistent nausea and vomiting. All 12 patients passed the DBPCFC at week 32 and continued to eat 10 to 20 peanuts daily until the end of the study. This study suggests that omalizumab may be a useful adjunct in OIT but that intolerable symptoms requiring the discontinuation of OIT still occurred.

SLIT

In SLIT, the food protein is delivered sublingually in a liquid form, held for 2 min, and then swallowed. This form of immunotherapy is thought to capitalize on the tolerogenic antigen-presenting cells, Langerhans cells, which are present in the oral mucosa [47]. It is further thought that SLIT exposes the mucosal immune system to the food protein in its intact form, before possible epitopes are broken down through gastric digestion [48]. SLIT doses, however, are limited by the concentration of available extracts and the volume of liquid that can be held under the tongue. Thus, typical doses will start with microgram levels of the allergenic protein and increase to milligram doses by maintenance. Studies examining SLIT for specific foods will be described below and are listed in Table 2.

Milk

In contrast to the numerous published studies examining milk OIT, only one study has examined the use of exclusively SLIT in milk allergy. In 2006, de Boissieu published a proof-of-concept study, in which eight children with confirmed milk allergy underwent milk SLIT to a goal dose of 1 mL/day of cow's milk over 6 months [49]. Six of the eight children completed the protocol, but only three (38 %) were able to consume 200 mL of milk without symptoms at the final DBPCFC.

Peanut

Two DBPC randomized trials for peanut SLIT were published over the last 3 years. The first enrolled 18 children randomized

Table 2 Studies examining sublingual immunotherapy (SLIT) for the treatment of food allergy

Study (year)	Food	Blinded	No. of subjects (age range)	Maintenance dose	Challenge dose[a]	Efficacy [*n* (%)][b]	Withdrawals [*n* (%)]	Tolerance [*n* (%)][c]
De Boissieu et al. (2006) [49]	Milk	No	8 (>6)	1 mL/day	200 mL	7/8 (87)	1/8 (13)	NA
Kim et al. (2011) [50]	Peanut	Yes	11 (2–10)	2.5 mg/day	2500 mg	11/11 (100)	0/11 (0)	NA
Fleischer et al. (2013) [51•]	Peanut	Yes	20 (12–36) 17 (12–36)	1.4 mg/day 3.7 mg/day	2500 mg	14/20 (70) 15/17 (88)	5/20 (25) 5/20 (25)	NA
Enrique et al. (2005) [52]	Hazelnut	Yes	23 (19–53)	13.25 mg/day	20 g	11/12 (92)	1/12 (8)	NA
Fernandez-Rivas et al. (2009) [53]	Peach	Yes	37 (18–65)	0.01 mg 3×/week	3.249 mg	33/37 (89)	4/37 (11)	NA
SLIT versus OIT								
Keet et al. (2012) [29••]	Milk	No	30 (6–17)	7 mg	8000 mg	1/10 (10)	2/10 (20)	1/10 (10)
				1000 mg/day		6/10 (60)		3/10 (30)
				2000 mg/day		8/10 (80)		5/10 (50)
Chin et al. (2013) [54•]	Peanut	Yes	27 (2–11) 23 (3–10)	2 mg/day 4000 mg/day	2500 mg 5000 mg	14/27 (52) 16/23 (70)	0/27 (0) 5/23 (22)	NA

NA not assessed

[a] Defined as the DBPCFC cumulative dose of the targeted food at the end of the desensitization protocol

[b] Defined as the number of subjects who successfully finished treatment and were able to include the targeted food in their diet or passed the post-treatment challenge after desensitization

[c] Defined as the number of children who passed a tolerance DBPCFC among those who started desensitization

to SLIT with a goal daily dose of 2500 μg (n=11) or a placebo (n=7). All 11 children in active therapy completed the desensitization protocol, and the median dose of peanut in the post-treatment DBPCFC was 1710 mg, compared to 85 mg for the placebo group [50].

Shortly thereafter, the CoFAR group randomized 40 adolescents and adults to peanut SLIT with a maximum dose of 1386 μg/day (n=20) or a placebo (n=20). After 44 weeks of active treatment, all subjects underwent a 5000-mg DBPCFC to peanut, and the placebo group crossed over to receive a maximum of 3696 μg daily. At this OFC, 14/20 individuals on active therapy were considered "responders," meaning that they could consume either 5 g of peanut or tenfold higher doses than their entry DBPCFC. The median tolerated dose in this group increased from 3.5 to 496 mg after treatment, compared to 71 mg in the placebo group, which was not significantly different. After six additional months of active therapy, the median tolerated peanut dose increased further to 996 mg. For the placebo-treated subjects who crossed over to a higher-dose SLIT, after 44 weeks, 7 of the 17 receiving treatment were "responders," with the median dose in this group increasing from 71 to 603 mg [51•]. The authors concluded that peanut SLIT induced a modest level of desensitization in most of the children, and it appeared that the longer duration of treatment was more efficacious.

Other Foods

Enrique et al. performed the first DBPC randomized trial for the treatment of food allergy, in which 29 individuals were randomized to active treatment with hazelnut extract (n=12) or a placebo (n=11) [52]. After 8–12 weeks of treatment, 11 individuals reached the target dose, and 5 of these 11 (42 %) were able to ingest 20 g of hazelnut in a DBPCFC without symptoms. In contrast, only 1 of the 11 individuals in the placebo group was able to ingest 20 g. While only 42 % of subjects receiving the active treatment were able to eat hazelnut ad lib, the mean tolerated dose increased from 2.29 to 11.56 g.

In 2009, Fernandez-Rivas et al. examined the use of SLIT for treatment of peach allergy using a Pru p 3 extract [53]. Fifty-six individuals were randomized to active treatment (n=37) with a goal of 10 μg of Pru p 3 three times weekly or a placebo (n=19). After 6 months of active treatment, 33 individuals completed the therapy, and 32 individuals were able to tolerate the maintenance dose. Compared to the placebo, this group was able to tolerate three- to nine-fold higher doses of peach after therapy.

Safety

In the above studies, SLIT was very well tolerated. The majority of patients experienced symptoms from this treatment, but they predominantly complained of local oropharyngeal itching, which typically resolved without treatment. Fleischer et al. reported that 63 % of 10,855 doses received were symptom free, and this increased to 94 % when oropharyngeal symptoms were excluded [51•]. Systemic symptoms were very rare [52], and most adverse reactions occurred during the initial buildup phase [50].

OIT Versus SLIT

Only two studies have directly compared OIT to SLIT [29••, 54•], and only one of those was conducted prospectively. In 2012, Keet et al. compared SLIT to OIT in an open-label, randomized trial of children with milk allergy. Thirty children underwent at least 6 weeks of initial SLIT to a goal dose of 3.7 mg of milk protein and were then randomized into three groups for further dose escalation: SLIT (goal dose 7 mg/day), OITA (goal dose 2 g/day), and OITB (goal dose 1 g/day). The children continued on the maintenance dose for 48 weeks and then underwent a DBPCFC to 8 g of cow's milk protein. The children who passed this challenge were then instructed to avoid milk for the next week, at which time they had a repeat DBPCFC. If the child passed this challenge, they avoided milk for another 5 weeks and returned for a final DBPCFC [29••].

The authors found that OIT was more efficacious than SLIT in inducing desensitization to cow's milk protein. While the food challenge threshold increased in all children on SLIT and OIT, this increase was more striking in the OIT groups. Whereas the threshold in the SLIT group increased sevenfold at 12 weeks, it increased 79-fold and 64-fold among the OIT children (OITA and B, respectively). At 60 weeks, this further increased to 40-fold among the SLIT group, versus 54-fold and 159-fold among the OIT groups (A and B, respectively).

The study further assessed whether SLIT or OIT was more likely to induce a state of sustained unresponsiveness. At 68 weeks of treatment, one of ten children in the SLIT group, six of ten in OITB (1 g/day), and eight of ten in OITA (2 g/day) passed the DBPCFC and were instructed to avoid milk. After 1 week of avoidance, two children in the OITB group reacted in the repeat DBPCFC. The other children continued to avoid milk for five more weeks, and at the final challenge, one child in the SLIT group, three children in OITB, and five children in OITA demonstrated sustained unresponsiveness. The authors further note that two children reacted after just 1 week of avoidance, highlighting the fact that individuals should continue on an inclusionary diet for an indefinite period of time after treatment.

With regard to safety, they found that while the overall reaction rate was similar among children undergoing SLIT and OIT (29 v. 23 %, respectively), the reactions during OIT were more likely to involve multiple systems, upper and lower respiratory tracts, and the gastrointestinal tract. Furthermore, there was more need for the use of beta-agonists and antihistamines in reactions with OIT compared to SLIT [29••]. The authors thus concluded that while OIT was found to be more efficacious, this treatment was accompanied by more systemic side effects.

In the second study, Chin et al. performed a retrospective study, comparing the results of two previously published SLIT and OIT protocols for peanut allergy. Twenty-seven children underwent peanut SLIT to a goal dose of 2 mg/day, and 23 children were treated with peanut OIT to a goal dose of 4000 mg/day. After 12 months of therapy, the children underwent a DBPCFC to 2500 mg (SLIT) and 5000 mg (OIT) [54•].

Similar to Keet et al., the authors found that OIT was more efficacious than SLIT for inducing desensitization to peanut protein. Of the 23 children who underwent OIT, 18 completed the desensitization protocol and 16 passed the DBPCFC after 1 year of therapy (70 %). In contrast, while all 27 children in the SLIT group completed the therapy, only eight (30 %) passed the 1-year DBPCFC. Even despite the lower challenge dose in the SLIT group, the authors found that OIT subjects were three times more likely to pass a DBPCFC after treatment than those undergoing SLIT (RR 3.00; 95 % CI 1.64–5.49) [54•].

Comparison of Mechanisms

While both SLIT and OIT have been shown to induce immunologic changes consistent with desensitization, children undergoing OIT were found to have a more profound drop in food-specific IgE [29••], a higher increase in food-specific IgG4 [54•], decreased basophil spontaneous histamine release [29••], and decreased CD63-upregulated basophils upon peanut allergen stimulation [54•] at 1 year. Children undergoing both SLIT and OIT to milk were found to have decreased skin prick test reactivity to milk after therapy [29••, 54•].

Conclusion

Recent advances in food immunotherapy research have given many patients and practitioners hope for a widely available treatment for food allergy. The studies presented in this review demonstrate that desensitization can be achieved in many patients undergoing either OIT or SLIT. Whereas individuals on OIT appear to reach higher challenge thresholds, have greater changes in immunologic measures of desensitization, and have a higher chance of achieving sustained unresponsiveness than those on SLIT, this is accompanied by an increase in the risk of both systemic reactions and intolerable gastrointestinal symptoms during treatment.

While the studies conducted to date are promising, many risks need to be addressed before food immunotherapy should be used in clinical practice. Systemic reactions are known to occur unpredictably during treatment, and at present, it does not appear that food immunotherapy decreases the risk of systemic reactions compared to those practicing food avoidance. It is also unclear whether food immunotherapy, which requires frequent visits and close follow-up, is a cost-effective treatment compared to food avoidance. Finally, little is known

about the optimal duration or long-term efficacy of these therapies, potentially leaving treated patients at high risk of subsequent reactions with even brief lapses in exposure. Thus, while these therapies are promising, further research to optimize therapy and reduce risk is clearly needed.

Compliance with Ethics Guidelines

Conflict of Interest Emily C. McGowan reports no conflict of interest. Robert A. Wood reports grants from NIH and royalties from Up to Date.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Sicherer SH. Epidemiology of food allergy. J Allergy Clin Immunol. 2011;127:594–602.
2. Sicherer SH, Munoz-Furlong A, Godbold JH, Sampson HA. US prevalence of self-reported peanut, tree nut, and sesame allergy: 11-year follow-up. J Allergy Clin Immunol. 2010;125:1322–6.
3. Venter C, Hasan Arshad S, Grundy J, et al. Time trends in the prevalence of peanut allergy: three cohorts of children from the same geographical location in the UK. Allergy. 2010;65:103–8.
4. Savage JH, Limb SL, Brereton NH, Wood RA. The natural history of peanut allergy: extending our knowledge beyond childhood. J Allergy Clin Immunol. 2007;120:717–9.
5. Savage JH, Matsui EC, Skripak JM, Wood RA. The natural history of egg allergy. J Allergy Clin Immunol. 2007;120:1413–7.
6. Skolnick HS, Conover-Walker MK, Koerner CB, Sampson HA, Burks W, Wood RA. The natural history of peanut allergy. J Allergy Clin Immunol. 2001;107:367–74.
7. Fleischer DM, Perry TT, Atkins D, et al. Allergic reactions to foods in preschool-aged children in a prospective observational food allergy study. Pediatrics. 2012;130:e25–32.
8. Yu JW, Kagan R, Verreault N, et al. Accidental ingestions in children with peanut allergy. J Allergy Clin Immunol. 2006;118:466–72.
9. Flokstra-de Blok BM, Dubois AE, Vlieg-Boerstra BJ, et al. Health-related quality of life of food allergic patients: comparison with the general population and other diseases. Allergy. 2010;65:238–44.
10. Akdis M, Akdis CA. Mechanisms of allergen-specific immunotherapy: multiple suppressor factors at work in immune tolerance to allergens. J Allergy Clin Immunol. 2014;133:621–31.
11. Oppenheimer JJ, Nelson HS, Bock SA, Christensen F, Leung DY. Treatment of peanut allergy with rush immunotherapy. J Allergy Clin Immunol. 1992;90:256–62.
12. Nelson HS, Lahr J, Rule R, Bock A, Leung D. Treatment of anaphylactic sensitivity to peanuts by immunotherapy with injections of aqueous peanut extract. J Allergy Clin Immunol. 1997;99:744–51.
13. Vickery BP, Scurlock AM, Jones SM, Burks AW. Mechanisms of immune tolerance relevant to food allergy. J Allergy Clin Immunol. 2011;127:576–84. *quiz 85–6*.
14. Patriarca G, Schiavino D, Nucera E, Schinco G, Milani A, Gasbarrini GB. Food allergy in children: results of a standardized protocol for oral desensitization. Hepato-Gastroenterology. 1998;45:52–8.
15. Meglio P, Bartone E, Plantamura M, Arabito E, Giampietro PG. A protocol for oral desensitization in children with IgE-mediated cow's milk allergy. Allergy. 2004;59:980–7.
16. Longo G, Barbi E, Berti I, et al. Specific oral tolerance induction in children with very severe cow's milk-induced reactions. J Allergy Clin Immunol. 2008;121:343–7.
17. Skripak JM, Nash SD, Rowley H, et al. A randomized, double-blind, placebo-controlled study of milk oral immunotherapy for cow's milk allergy. J Allergy Clin Immunol. 2008;122:1154–60.
18. Pajno GB, Caminiti L, Ruggeri P, et al. Oral immunotherapy for cow's milk allergy with a weekly up-dosing regimen: a randomized single-blind controlled study. Ann Allergy Asthma Immunol Off Publ Am Coll Allergy Asthma Immunol. 2010;105:376–81.
19. Martorell A, De la Hoz B, Ibanez MD, et al. Oral desensitization as a useful treatment in 2-year-old children with cow's milk allergy. Clin Exp Allergy J Br Soc Allergy Clin Immunol. 2011;41:1297–304.
20. Garcia-Ara C, Pedrosa M, Belver MT, Martin-Munoz MF, Quirce S, Boyano-Martinez T. Efficacy and safety of oral desensitization in children with cow's milk allergy according to their serum specific IgE level. Ann Allergy Asthma Immunol Off Publ Am Coll Allergy Asthma Immunol. 2013;110:290–4.
21. Salmivesi S, Korppi M, Makela MJ, Paassilta M. Milk oral immunotherapy is effective in school-aged children. Acta Paediatr (Oslo, Norway : 1992). 2013;102:172–6.
22. Patriarca G, Nucera E, Roncallo C, et al. Oral desensitizing treatment in food allergy: clinical and immunological results. Aliment Pharmacol Ther. 2003;17:459–65.
23. Morisset M, Moneret-Vautrin DA, Guenard L, et al. Oral desensitization in children with milk and egg allergies obtains recovery in a significant proportion of cases. A randomized study in 60 children with cow's milk allergy and 90 children with egg allergy. Eur Ann Allergy Clin Immunol. 2007;39:12–9.
24. Brozek JL, Terracciano L, Hsu J, et al. Oral immunotherapy for IgE-mediated cow's milk allergy: a systematic review and meta-analysis. Clin Exp Allergy J Br Soc Allergy Clin Immunol. 2012;42:363–74.
25.• Yeung JP, Kloda LA, McDevitt J, Ben-Shoshan M, Alizadehfar R. Oral immunotherapy for milk allergy. Cochrane Database Syst Rev. 2012;11, CD009542. *In this systematic review and meta-analysis, the authors concluded that while OIT for milk allergy appears to be efficacious, the quality of evidence is low due to small studies with inconsistent methodology.*
26. Meglio P, Giampietro PG, Gianni S, Galli E. Oral desensitization in children with immunoglobulin E-mediated cow's milk allergy—follow-up at 4 yr and 8 months. Pediatr Allergy Immunol Off Publ Eur Soc Pediatr Allergy Immunol. 2008;19:412–9.
27.• Keet CA, Seopaul S, Knorr S, Narisety S, Skripak J, Wood RA. Long-term follow-up of oral immunotherapy for cow's milk allergy. J Allergy Clin Immunol. 2013;132:737–9.e6. *In a study examining the long-term efficacy of milk OIT, the authors found that 22% of patients ate only trace amounts of milk/baked milk or avoided milk completely 3–4 years after therapy.*
28. Narisety SD, Skripak JM, Steele P, et al. Open-label maintenance after milk oral immunotherapy for IgE-mediated cow's milk allergy. J Allergy Clin Immunol. 2009;124:610–2.
29.•• Keet CA, Frischmeyer-Guerrerio PA, Thyagarajan A, et al. The safety and efficacy of sublingual and oral immunotherapy for milk allergy. J Allergy Clin Immunol. 2012;129:448–55.e1-5. *In this randomized controlled trial comparing milk SLIT to OIT, the*

authors found that those undergoing OIT were more likely to develop desensitization to milk than those undergoing SLIT. Those on OIT, however, were also more likely to have systemic reactions during treatment than those on SLIT.

30. Buchanan AD, Green TD, Jones SM, et al. Egg oral immunotherapy in nonanaphylactic children with egg allergy. J Allergy Clin Immunol. 2007;119:199–205.
31. Vickery BP, Pons L, Kulis M, Steele P, Jones SM, Burks AW. Individualized IgE-based dosing of egg oral immunotherapy and the development of tolerance. Ann Allergy Asthma Immunol Off Publ Am Coll Allergy Asthma Immunol. 2010;105:444–50.
32. Garcia Rodriguez R, Urra JM, Feo-Brito F, et al. Oral rush desensitization to egg: efficacy and safety. Clin Exp Allergy J Br Soc Allergy Clin Immunol. 2011;41:1289–96.
33.•• Burks AW, Jones SM, Wood RA, et al. Oral immunotherapy for treatment of egg allergy in children. N Engl J Med. 2012;367:233–43. *In a randomized controlled trial comparing egg OIT to placebo, the authors found that egg OIT is efficacious in inducing clinical desensitization, and that efficacy appears to improve with longer duration of treatment.*
34. Meglio P, Giampietro PG, Carello R, Gabriele I, Avitabile S, Galli E. Oral food desensitization in children with IgE-mediated hen's egg allergy: a new protocol with raw hen's egg. Pediatr Allergy Immunol Off Publ Eur Soc Pediatr Allergy Immunol. 2013;24:75–83.
35. Clark AT, Islam S, King Y, Deighton J, Anagnostou K, Ewan PW. Successful oral tolerance induction in severe peanut allergy. Allergy. 2009;64:1218–20.
36. Jones SM, Pons L, Roberts JL, et al. Clinical efficacy and immune regulation with peanut oral immunotherapy. J Allergy Clin Immunol. 2009;124(292–300):e1–97.
37.• Varshney P, Jones SM, Scurlock AM, et al. A randomized controlled study of peanut oral immunotherapy: clinical desensitization and modulation of the allergic response. J Allergy Clin Immunol. 2011;127:654–60. *In this randomized controlled trial comparing peanut OIT to placebo, the efficacy of treatment for inducing clinical desensitization was 84 %.*
38.•• Anagnostou K, Islam S, King Y, et al. Assessing the efficacy of oral immunotherapy for the desensitisation of peanut allergy in children (STOP II): a phase 2 randomised controlled trial. Lancet. 2014;383:1297–304. *In a randomized controlled crossover trial of peanut OIT, the authors found that active OIT (maintenance dose 800 mg/day) resulted in desensitization in 84–91 % of treated children.*
39. Blumchen K, Ulbricht H, Staden U, et al. Oral peanut immunotherapy in children with peanut anaphylaxis. J Allergy Clin Immunol. 2010;126:83–91.e1.
40. Syed A, Garcia MA, Lyu SC, et al. Peanut oral immunotherapy results in increased antigen-induced regulatory T-cell function and hypomethylation of forkhead box protein 3 (FOXP3). J Allergy Clin Immunol. 2014;133:500–10.
41. Wasserman RL, Factor JM, Baker JW, et al. Oral immunotherapy for peanut allergy: multipractice experience with epinephrine-treated reactions. J Allergy Clin Immunol Pract. 2014;2:91–6.
42. Anagnostou K, Clark A, King Y, Islam S, Deighton J, Ewan P. Efficacy and safety of high-dose peanut oral immunotherapy with factors predicting outcome. Clin Exp Allergy J Br Soc Allergy Clin Immunol. 2011;41:1273–81.
43. Ridolo E, De Angelis GL, Dall'aglio P. Eosinophilic esophagitis after specific oral tolerance induction for egg protein. Ann Allergy Asthma Immunol Off Publ Am Coll Allergy Asthma Immunol. 2011;106:73–4.
44. Sanchez-Garcia S, Rodriguez Del Rio P, Escudero C, Martinez-Gomez MJ, Ibanez MD. Possible eosinophilic esophagitis induced by milk oral immunotherapy. J Allergy Clin Immunol. 2012;129:1155–7.
45. Nadeau KC, Schneider LC, Hoyte L, Borras I, Umetsu DT. Rapid oral desensitization in combination with omalizumab therapy in patients with cow's milk allergy. J Allergy Clin Immunol. 2011;127:1622–4.
46.• Schneider LC, Rachid R, LeBovidge J, Blood E, Mittal M, Umetsu DT. A pilot study of omalizumab to facilitate rapid oral desensitization in high-risk peanut-allergic patients. J Allergy Clin Immunol. 2013;132:1368–74. *In this pilot study, children with peanut allergy were treated with both OIT and omalizumab. The authors found that 92 % of patients were desensitized to peanut with this regimen.*
47. Akdis CA, Barlan IB, Bahceciler N, Akdis M. Immunological mechanisms of sublingual immunotherapy. Allergy. 2006;61 Suppl 81:11–4.
48. Untersmayr E, Jensen-Jarolim E. The role of protein digestibility and antacids on food allergy outcomes. J Allergy Clin Immunol. 2008;121:1301–8. *quiz 9–10.*
49. de Boissieu D, Dupont C. Sublingual immunotherapy for cow's milk protein allergy: a preliminary report. Allergy. 2006;61:1238–9.
50. Kim EH, Bird JA, Kulis M, et al. Sublingual immunotherapy for peanut allergy: clinical and immunologic evidence of desensitization. J Allergy Clin Immunol. 2011;127:640–6.e1.
51.• Fleischer DM, Burks AW, Vickery BP, et al. Sublingual immunotherapy for peanut allergy: a randomized, double-blind, placebo-controlled multicenter trial. J Allergy Clin Immunol. 2013;131:119–27.e1-7. *In this randomized controlled trial comparing peanut SLIT to placebo, the authors found that peanut SLIT induced a modest level of desensitization in most children, and this efficacy appeared to be related to duration of treatment.*
52. Enrique E, Pineda F, Malek T, et al. Sublingual immunotherapy for hazelnut food allergy: a randomized, double-blind, placebo-controlled study with a standardized hazelnut extract. J Allergy Clin Immunol. 2005;116:1073–9.
53. Fernandez-Rivas M, Garrido Fernandez S, Nadal JA, et al. Randomized double-blind, placebo-controlled trial of sublingual immunotherapy with a Pru p 3 quantified peach extract. Allergy. 2009;64:876–83.
54.• Chin SJ, Vickery BP, Kulis MD, et al. Sublingual versus oral immunotherapy for peanut-allergic children: a retrospective comparison. J Allergy Clin Immunol. 2013;132:476–8.e2. *In this retrospective study comparing peanut OIT to SLIT, the authors found that OIT was more efficacious than SLIT for inducing clinical desensitization. They also found that those on OIT had greater measures of immunologic desensitization than those on SLIT.*
55. Alvaro M, Giner MT, Vazquez M, et al. Specific oral desensitization in children with IgE-mediated cow's milk allergy. Evolution in one year. Eur J Pediatr. 2012;171:1389–95.
56. Levy MB, Elizur A, Goldberg MR, Nachshon L, Katz Y. Clinical predictors for favorable outcomes in an oral immunotherapy program for IgE-mediated cow's milk allergy. Ann Allergy Asthma Immunol Off Publ Am Coll Allergy Asthma Immunol. 2014;112:58–63.e1.
57. Staden U, Rolinck-Werninghaus C, Brewe F, Wahn U, Niggemann B, Beyer K. Specific oral tolerance induction in food allergy in children: efficacy and clinical patterns of reaction. Allergy. 2007;62:1261–9.