



Novel immunotherapy and treatment modality for severe food allergies

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Purpose of review

In recent years, many studies on oral immunotherapy (OIT) have been conducted; however, few have focused on severe food allergies. The purpose of this review was to assess the efficacy and safety of oral immunotherapies for patients with severe food allergy.

Recent findings

We reviewed multiple immunotherapy reports published within a few years or reports focusing on severe food allergies. We also investigated recent studies on OIT and novel food allergy management.

Summary

Immunotherapies targeting low-dose antigen exposure and oral food challenges using low-dose target volumes may be safer than conventional OIT. It is necessary to consider which immunotherapy regimen is appropriate based on allergy severity of the patient.

Keywords

adverse event, anaphylaxis, food allergy, oral immunotherapy, severe

INTRODUCTION

Prevalence of food allergy is increasing [1,2]. Although many patients with egg and milk allergies develop natural tolerance, some egg and milk allergies, and a majority of peanut and other nut allergies, are not outgrown [3–6]. Patients with a history of anaphylaxis are unlikely to acquire tolerance [7,8]. The principles of food allergy management are avoidance of trigger food(s) and prescription of rescue medication in the event of accidental allergen exposure [9]. In patients with severe food allergies, a trace amount of allergen exposure may lead to anaphylaxis [10] and reduced quality of life [11]. However, oral immunotherapy (OIT) for patients with a history of food-related anaphylaxis has not been clarified. Our objective is to review recent studies focusing on OIT management of severe food allergies.

PREVIOUS ORAL IMMUNOTHERAPY FOR SEVERE FOOD ALLERGY

In most OIT trials, protocols consist of three phases: an escalation phase, a build-up phase, and a maintenance phase. Table 1 summarizes the characteristics of multiple OIT studies focusing on allergies related to egg, milk, peanut, or wheat [12–23].

Efficacy of oral immunotherapy

In 2015, a randomized controlled trial (RCT) of egg OIT ($n = 31$) that involved a double-blind, placebo-controlled food challenge (DBPCFC) showed that, at baseline, 11% of patients with egg allergy had a history of anaphylaxis and 19% had experienced multisystem symptoms. After 4 months of OIT followed by 6 months of consuming an egg-containing diet, 29% of patients achieved sustained unresponsiveness after 3 months of avoidance in the OIT group. In the control group, 7% of patients achieved tolerance [15]. In 2017, Perez-Rangel *et al.* [17] also conducted a RCT focusing on egg OIT. In the OIT group, 32% of patients had a prior history of anaphylaxis, and the baseline median challenge

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KEY POINTS

- OIT induces desensitization in most patients, though few patients achieve sustained unresponsiveness and there is a possibility of severe adverse reactions.
- OIT targeting lower doses (SLIT, low-dose OIT) appears to be a well tolerated and effective treatment for patients with severe food allergy.
- Very low-dose OFCs may be more effective than strict elimination.
- It is necessary to consider which immunotherapy and treatment modality is appropriate, depending on the severity of patients.

threshold was 225 mg egg white protein. At 5 months, 89% of patients in the OIT group and none in the control group were desensitized to 2808 mg egg white protein.

Several studies have evaluated OIT for patients with severe peanut allergy [19,20,22]. In a study by Anagnostou *et al.*, [19] 99 patients with peanut allergy were randomly allocated to an OIT group or a control group. Baseline median threshold in both groups was 55 mg peanut protein. At 6 months, 62% of patients in the OIT group and none in the control group were desensitized to 1400 mg peanut protein. In 2014, a peanut-focused OIT study showed that, among patients with severe peanut allergy (87% with a history of anaphylaxis), median challenge threshold increased from 0.2 g peanut to 3.5 g or 7 g peanut [20].

Longo *et al.* [12] conducted a RCT focusing on milk OIT in 60 patients with milk allergy. The challenge threshold of DBPCFC was less than 0.1 ml milk in 15% of patients and 0.2–0.8 ml milk in 85% of patients. After 1 year, 36% of patients in the OIT group achieved desensitization to 150 ml milk, and none of the patients achieved desensitization in the control group. In 2017, Perezabad *et al.* [13] conducted a single-blind food challenge in 20 patients with milk allergy, of which 60% had a history of anaphylaxis. The median challenge threshold was 4.0 ml milk. Over an average of 18 months, 70% of patients were desensitized to more than 200 ml milk. The first OIT trial focusing on milk allergy using microwave heated cow's milk was published in 2016. Upon intake of 2 ml unheated cow's milk (median challenge threshold), 19% of patients developed grade 3 symptoms and 13% developed grade 4 symptoms per Sampson anaphylaxis criteria. For the OIT protocol, patients were given cow's milk which was warmed in a microwave oven at 550 W for 100 s. After 12 months

from the start of OIT, 21% of patients achieved 2 week sustained unresponsiveness to 200 ml milk [14].

Wheat OIT for patients with wheat-related anaphylaxis was first reported by Sato *et al.* [23] in 2015. In this study, anaphylaxis was confirmed in all 18 patients by performing DBPCFC, in which the median challenge threshold was 80 mg of wheat protein. After 48 months, 61% of patients were confirmed to have achieved sustained unresponsiveness to 5200 mg of wheat protein after cessation of OIT for 2 weeks.

Data suggests that OIT for patients with severe food allergy induces desensitization in a majority of patients; however, few achieve sustained unresponsiveness. Moreover, OIT outcomes may differ depending on the food allergen and symptom severity [24].

Safety of oral immunotherapy

Adverse clinical events, including anaphylaxis, may develop during OIT [25,26]. For example, in a RCT of egg OIT in 2017, two cases of anaphylaxis required the use of intramuscular adrenaline [17]. In another RCT focusing on peanut OIT, β_2 inhalation was administered 63 times (0.35% of doses) and intramuscular adrenaline was administered twice during OIT [19]. Another OIT for severe peanut allergy demonstrated that during the rush phase, 12% of ingestions resulted in allergic symptoms requiring treatment, of which one patient received intramuscular adrenaline. During the maintenance phase, two additional patients experienced anaphylaxis [20]. In a wheat OIT trial, the ratio of doses per participant with symptoms requiring treatment was 11% during the rush phase, 2.6% at home and three patients required intramuscular adrenaline at home [23].

There appears to be an increased frequency of adverse clinical events associated with milk OIT compared with OIT for other common food allergens. In one RCT on milk OIT, four patients showed severe symptoms requiring intramuscular adrenaline [12]. In 2016, an OIT study using heated cow's milk demonstrated that the average rate of adverse clinical events per dose per child was 1.7% (grade 3 symptoms) and 0.2% (grade 4 symptoms) in the hospital, and 1% (grade 3 symptoms) and 0.04% (grade 4 symptoms) at home. Intramuscular adrenaline was administered six times in the hospital and nine times at home [14]. Given the possibility of a severe adverse reaction to a food allergen, it is necessary to establish a well tolerated OIT protocol for patients with severe food allergy [12,28].

From these reports, we find that during OIT for severe food allergy, most of the patients experience

Table 1. Previous oral immunotherapy for severe food allergy

Antigen	Author	Sample size	Age [years (range)]	Severity of patients	Maintenance dose	Duration (months)	Results
Cow's milk	Longo <i>et al.</i> (2008) [12]	OIT: 30 Control: 30	7.9 (5–17)	All study participants had a history of severe allergic reaction	150 ml of milk	12	Desensitization: OIT 36% (11/30), placebo 0% (0/30)
	Perezabad <i>et al.</i> (2017) [13]	OIT: 20	4.3 (1–11)	60% (12/20) developed anaphylactic symptoms in the OFC	200 ml of milk	18	Desensitization to 200 ml of milk: OIT 70% (14/20)
	Takahashi <i>et al.</i> (2016) [14]	OIT: 31	9 (5–11)	71% (22/31) had a history of anaphylaxis	200 ml of milk	12	Desensitization: 45% (14/31). SU to 200 ml of milk: OIT 25% (8/31)
	Caminiti <i>et al.</i> (2015) [15]	OIT: 17	6 (4–10)	11% (2/17) had a history of anaphylaxis	4 g of dehydrated egg white	4 month of OIT and 6 month of diet	Desensitization: OIT 94% (16/17), placebo 0% (0/14). SU after 3 months of avoidance: OIT 29% (5/17), placebo 0% (0/14)
Hen's egg	Burks <i>et al.</i> (2012) [16]	Placebo: 14	6 (4–11)	Study participants with a history of severe anaphylaxis were excluded	1/3 of a whole egg	22	Desensitization: OIT 75% (30/40), placebo 0% (0/15). SU after 4–6 week avoidance: OIT 28% (11/40), placebo 0% (0/15)
		OIT: 40	7.0 (5–11)				
	Perez-Rangel <i>et al.</i> (2017) [17]	Placebo: 15 OIT: 19	7.0 (5–11) 6–16	42% (14/33) had a history of anaphylaxis	2808 mg of egg white protein	5	Desensitization: OIT 89% (17/19), control 0% (0/13)
	Akashi <i>et al.</i> (2016) [18]	Control: 13 OIT: 18	5.0 (4–8)	Median threshold at DBPCFC: 250 mg of egg protein	1/4 of raw egg	6	Desensitization: OIT 57% (14/18), control 0% (0/16)
Peanut	Anagnostou <i>et al.</i> (2014) [19]	OIT: 39	12.3 (8–16)	Worst clinical reaction (assessed by WAO score): G1 40.8%, G2 51%, G3 6.1%, G4 2%	800 mg of peanut protein	6	Desensitization to 1400 mg of peanut protein: OIT 62% (24/39), placebo 0% (0/46)
		Placebo: 46	12.3 (7–16)				
	Nozawa <i>et al.</i> (2014) [20]	OIT: 16	9 (5–14)	87% (14/16) had a history of anaphylaxis	3.5 g or 7 g of peanut	36	Desensitization: OIT 100% (16/16)
	Vickery <i>et al.</i> (2014) [21]	OIT: 24	1–16	Study participants with peanut-related anaphylaxis were excluded	4 g of peanut protein	Up to 60 month (mean 1453 days)	SU to 5 g of peanut protein after 4 week avoidance: OIT 50% (12/24)
Wheat	Tang <i>et al.</i> (2015) [22]	OIT with adjuvant probiotic: 31	6.1	45% (14/31) had a history of anaphylaxis	2 g of peanut protein	18	SU to 2 g of peanut protein after 2–5 week avoidance: OIT 74% (23/31), placebo 3.2% (1/31)
	Sato <i>et al.</i> (2015) [23]	Placebo: 31	5.8	94% (17/18) developed severe symptoms according to the anaphylaxis guidelines of the EAACI at baseline OFC.	5.2 g of wheat protein	24	SU to 5.2 g of wheat protein after 2 week avoidance: OIT 61% (11/16), control 9% (1/11)
		OIT: 18	9.0 (5–13)				
		Control: 11	7.0 (5–9)				

EAACI, European Academy of Allergy and Clinical Immunology; OFC, oral food challenge; OIT, oral immunotherapy; SU, sustained unresponsiveness.

any adverse reactions. These reactions are mainly mild or moderate, but at times can be severe, requiring the use of intramuscular adrenaline.

NOVEL ORAL IMMUNOTHERAPY APPROACHES FOR SEVERE FOOD ALLERGY

One challenge facing allergists and immunologists is the increased frequency of adverse clinical events observed among patients undergoing OIT with a history of severe food allergy. Recently, several OIT trials focusing on adjunctive therapies and low-dose target doses were investigated for the purpose of improving efficacy and safety of OIT for severe food allergy [27–33]. (Table 2)

Oral immunotherapy with anti-IgE

In recent years, some studies have incorporated anti-immunoglobulin E (IgE) mAb (omalizumab) with OIT [27–29]. In 2016, the first RCT of omalizumab combined with OIT was reported. After 4 months of omalizumab or placebo administration, an escalation phase of milk OIT was initiated, followed by a daily maintenance phase (3.8 g milk protein) for a total of 28 months, after which omalizumab was discontinued and sustained unresponsiveness was assessed 4 months later. Results showed that the rate of desensitization to 10 g milk protein and sustained unresponsiveness after a 8-week avoidance was not significantly different between the active and the placebo groups. Regarding safety, the rate of adverse events and those requiring treatment were significantly lower in the omalizumab group (2%, 0%) than the placebo group (16%, 4%) during the escalation period [28]. These results suggest that omalizumab with OIT may improve safety; however, is unlikely to change OIT outcome.

Low-dose oral immunotherapy

A few recent studies have demonstrated the efficacy and safety of low-dose OIT [30–33]. A study by Yanagida *et al.* [30] showed that, after 12 months of low-dose OIT (3 ml milk), 33% of patients with severe milk allergy experienced sustained unresponsiveness to 25 ml milk after a 2-week allergen avoidance period. A low-dose OIT study for patients with severe egg allergy showed that, after a build-up phase, the volume was gradually increased to 194 mg egg protein (1/32 whole egg). At 12 months, 33% of patients in the low-dose OIT group experienced sustained unresponsiveness to 1/2 whole egg after 2 weeks of allergen avoidance, compared with 0% of patients in the control group. Compared with

conventional OIT, the frequency of moderate-to-severe symptoms, including those requiring treatment, were lower with low-dose OIT [24,31]. In a study by Vickery *et al.* [32] on low-dose peanut OIT, 37 patients with severe peanut allergy were randomized to receive either low-dose OIT (300 mg peanut protein/day) or high-dose OIT (3000 mg peanut protein/day). Over a median of 29 months, 85% of patients in the low-dose OIT group and 71% in the high-dose OIT group showed sustained unresponsiveness to 5 g peanut protein after a 4-week avoidance period.

These data suggest that low-dose OIT may be a relatively well tolerated and effective treatment to induce sustained unresponsiveness for severe food allergy patients.

ALTERNATIVE IMMUNOTHERAPIES

Sublingual immunotherapy

Sublingual immunotherapy (SLIT) has been efficacious not only for bronchial asthma and allergic rhinitis, but also for food allergy. Several studies have shown that SLIT for various food allergens, including peanut, milk, kiwi, peach, and hazelnut, is associated with increased challenge thresholds and milder adverse clinical reactions [34–39]. (Table 3) In 2015, a double-blind placebo-controlled study by Narisety *et al.* [38] aimed to compare the efficacy and safety of SLIT for peanut. In total, 21 patients were randomized to receive active SLIT/placebo OIT or active OIT/placebo SLIT. Five patients discontinued therapy during the blinded phase. After 12 months, all 16 patients had a greater than 10-fold increase in challenge threshold, which was significantly greater in the active OIT group. Adverse reactions were more common in the active OIT group, including reactions requiring medication treatment. These results were similar to those of the milk SLIT study [34]. These data suggested that SLIT is safer, however not as effective as OIT.

Epicutaneous immunotherapy

Only two clinical trials have been published on the efficacy of epicutaneous immunotherapy (EPIT) for milk or peanut [40,41] (Table 3). In a pilot trial, patients who displayed an allergic reaction to less than 10 ml cow's milk were randomized to an active (EPIT) group or a placebo group. After 3 months, the challenge threshold appeared to increase in the active group compared with the placebo group. Adverse reactions were mostly mild dermatologic reactions that did not require treatment or cessation in therapy [40].

Table 2. Novel approaches of oral immunotherapy for severe food allergy

Antigen	Author	Sample size	Age [years (range)]	Severity of patients	Maintenance dose	Duration (months)	Results
Omalizumab combined with OIT	Schneider <i>et al.</i> [2013] [27]	OIT: 13	7–15	Median threshold at DBPCFC: 2.5 mg of peanut protein	4000 mg of peanut flour	8	Desensitization: 92% (12/13)
	Wood <i>et al.</i> [2016] [28 ^a]	Combined with Omalizumab: 27	11.7 (9–15)	Threshold at DBPCFC is <2 g of milk protein	3800 mg of milk protein	28	SU to 10 g after 8 week avoidance: Omalizumab 48%, Placebo 35%; adverse reaction rate was 2.1% vs. 16.1%.
	Calatayud <i>et al.</i> [2016] [29]	Placebo: 29 Milk OIT: 5	9.5 (8–13) 3–13	79% (11/14) had a history of anaphylaxis	200 ml of milk, 1.8 g of egg protein	12	All patients were desensitized
Low-dose OIT	Egg OIT: 9						
	Yanagida <i>et al.</i> [2015] [30]	OIT: 12	8.3 (6–12)	Median threshold of objective symptoms: 1.6 ml (0.75–3) of milk	3 ml of milk	12	SU to 25 ml of milk after 2 week avoidance: OIT 33% (4/12), Control 0% (0/25)
	Yanagida <i>et al.</i> [2016] [31]	Control: 25 OIT: 21	7.3 (5–9) 8.7 (6–18)	Median threshold of objective symptoms: 194 mg (52–194) of egg protein	194 mg of egg protein (1/32 of egg)	12	SU to 1/2 of egg after 2 week avoidance: OIT 33% (7/23), Control 0% (0/12)
Peanut	Vickery <i>et al.</i> [2017] [32 ^a]	Control: 12 Low-dose OIT: 20	7.0 (5–12) 9–36 months	Peanut allergic or sensitized patients	Low: 300 mg of peanut protein,	29	SU to 5 g of peanut protein after 4 week avoidance: low-dose 85% (17/20), high-dose 71% (12/17)
	Blumchen <i>et al.</i> [2010] [33]	High-dose OIT: 17 Low-dose OIT: 23	5.6 (3–14)	Maximum tolerated dose: 190 mg (20–1000) of peanut	High: 3000 mg of peanut protein 500 mg of peanut	Up to 22 months	Desensitization to 0.5 g of peanut: 61% (14/23). SU to 3 g: 13% (3/23)

DBPCFC, double-blind, placebo-controlled food challenge; OIT, oral immunotherapy; SU, sustained unresponsiveness.

Table 3. Alternative immunotherapies to oral immunotherapy and very low-dose oral food challenge

Antigen	Author	Sample size	Age [Years (range)]	Severity of patients	Maintenance dose	Duration (months)	Results
SLIT	Narisety <i>et al.</i> (2015) [38]	SLIT: 10	11.1 (7–12)	10% (1/10) had a history of anaphylaxis	SLIT: 3.7 mg of peanut protein,	12	Median threshold increased from 21 to 496 mg (SLIT) and from 21 to 7246 mg (OIT). Symptoms were more severe with OIT than with SLIT.
		OIT: 10	11.1 (9–13)		OIT: 2000 mg of peanut protein		
	Burks <i>et al.</i> (2015) [39]	SLIT: 20	14 (13–18)	SCD: 6 mg of peanut protein	SLIT: 1386 µg or 3696 µg (high dose) of peanut protein	36	SU to 10 g of peanut after 8 week avoidance: 10% (4/37)
		High-dose SLIT: 20	16 (14–18)				
	Keet <i>et al.</i> (2012) [34]	SLIT: 10	8 (6–11)	80% (8/10) had a history of anaphylaxis	SLIT: 7 mg of cow's milk protein,	60 weeks	Desensitization to 8 g of cow's milk protein: SLIT 10% (1/10), OIT 70% (14/20). Symptoms requiring treatment were more severe with OIT than with SLIT.
EPIT	Hazelhut Enrique <i>et al.</i> (2005) [37]	SLIT: 12	29.2 (19–53)	Patients had a history of allergic reaction	SLIT: 13.25 mg of hazelnut protein	8–12 weeks	Mean threshold increased from 2.29 g to 11.56 g in the SLIT group.
		Placebo: 11	29.6 (19–42)		OIT: 1000 mg or 2000 mg of cow's milk protein		
	Dupont <i>et al.</i> (2010) [40]	EPIT: 10	3.8 (0.8–7.6)	SCD: <10 ml of milk	EPIT: 1 mg skimmed cow's milk powder	3	50% (5/10) achieved a 10-fold increase in SCD at 3 months
	Jones <i>et al.</i> (2016) [41]	Placebo: 9					
		EPIT: 49	8.2 (4.1–20.3)	Study participants with a history of anaphylaxis were excluded.	EPIT: 100 µg or 250 µg of peanut protein	52 weeks	47% (23/49) achieved a 10-fold or greater increase in SCD at 52 weeks
Very Low-dose OFC	Okada <i>et al.</i> (2015) [42]	Placebo: 25					
		VL tolerant: 41	4.3 (1–12)	59% (49/83) had a history of anaphylaxis	3 ml of cow's milk	12	Consumption of 25 ml of cow's milk: VL tolerant 45%, VL reactive 0%
	Okada <i>et al.</i> (2016) [43]	VL reactive: 42	4.0 (1–8)				
		VL tolerant: 32	2.0 (1–11)	46% (26/57) had a history of anaphylaxis	53 mg of wheat protein	12	Consumption of 400 mg of wheat protein: VL tolerant 56%, VL reactive 0%
	Okada <i>et al.</i> (2016) [44]	VL reactive: 25 EYSEW tolerant: 179 EYSEW reactive: 18	3.8 (1–6) 18 months (12–23 months) 19 months (12–23 months)	10% had a history of anaphylaxis	1/35 of whole egg	36	Heated hen's egg tolerant: EYSEW tolerant 92%, EYSEW reactive 67%

EPIT, epicutaneous immunotherapy; EYSEW, egg yolk slightly contaminated with egg white; OFC, oral food challenge; OIT, oral immunotherapy; SCD, successfully consumed dose; SLIT, sublingual immunotherapy; SU, sustained unresponsiveness; VL, very low dose.

In a 2016 double-blind placebo-controlled study by Jones *et al.*, [41] 74 patients with peanut allergy were randomized to receive placebo, 0.1 mg peanut protein, or 0.25 mg peanut protein. After 52 weeks, the proportion of 10-fold increase in successfully consumed dose from baseline in both EPIT groups were significantly higher than the placebo group. However, no patient in the EPIT group passed the oral food challenge (OFC) of 5044 mg peanut protein. Peanut-specific immunoglobulin G4 (IgG4) levels and IgG4/IgE ratios increased in those undergoing EPIT. The majority of adverse events were mild skin reactions limited to the test site.

Although EPIT is safer than conventional immunotherapy for food allergy, the therapeutic effect is mild.

In summary, the above studies showed that OIT appears to induce desensitization among patients with severe food allergy; however, long-term sustained unresponsiveness is not always achieved. Additionally, it is possible that moderate to severe symptoms, including those requiring intramuscular adrenaline, may occur with OIT. Therefore, low-dose OIT, SLIT, or EPIT may be safer than conventional OIT for severe food allergy.

EARLY INTERVENTION TO PREVENT STRICT ELIMINATION

Recent studies have shown that very low-dose OFCs are efficacious for avoiding strict elimination of food allergens [24,42–44]. (Table 3) In a 2015 study by Okada *et al.*, patients with severe milk allergy underwent very low-dose OFC with 3 ml of heated milk. If patients passed the very low-dose OFC, they were advised to consume 3 ml of milk at least once weekly at home. Of the patients who tolerated the challenge threshold, 45% were able to consume 25 ml of heated milk within 1 year [42]. In another study by Okada *et al.*, [43] 57 patients with severe wheat allergy (challenge threshold <400 mg wheat protein) underwent very low-dose OFC with 53 mg wheat protein. Of the 32 patients who passed the very low-dose OFC, 56% were able to consume 400 mg wheat protein within 1 year. A study on very low-dose OFC for egg reported that, of 197 patients with egg allergy, 91% initially passed an OFC of egg yolk slightly contaminated with egg white. After 36 months, 92% of patients achieved tolerance [44].

CONCLUSION

Severity of adverse reactions and low rates of achieving sustained unresponsiveness are two challenges commonly faced by researchers studying OIT for patients with severe food allergy. Low-dose OIT,

SLIT, and EPIT are alternative therapies that appear to not only be effective, but also result in milder adverse events, although optimal sustained unresponsiveness is not always achieved. Given the propensity of side-effects in patients with severe food allergy, treating with the smallest effective target dose is ideal, and may even accelerate allergen tolerance. It is recommended that clinicians individualize immunotherapy and management based on symptom severity of the patient. Although OIT cannot be recommended for routine clinical practice yet, results are promising for future treatment of severe food allergy.

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Conflicts of interest

There are no conflicts of interest.

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- of special interest
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