Review

International Archives of Allergy and Immunology

Int Arch Allergy Immunol 2014;164:1–9
DOI: 10.1159/000361025

Published online: April 29, 2014

Clinical Studies in Oral Allergen-Specific Immunotherapy: Differences among Allergens

Sakura Sato[a] Noriyuki Yanagida[b] Kiyotake Ogura[a] Takanori Imai[a, c] Tomohiro Utsunomiya[a, d] Katsuhito Iikura[b] Makiko Goto[a, e] Tomoyuki Asaumi[b] Yu Okada[b] Yumi Koike[b] Akinori Shukuya[b] Motohiro Ebisawa[a]

[a]Clinical Research Center for Allergy and Rheumatology, and [b]Department of Pediatrics, Sagamihara National Hospital, Sagamihara, [c]Department of Pediatrics, Showa University, Tokyo, [d]Department of Pediatrics, Takasaki National Hospital, Gunma, and [e]Department of Pediatrics, Beppu National Hospital, Oita, Japan

Key Words
Desensitization · Food allergy · Oral immunotherapy · Oral tolerance

Abstract
Oral immunotherapy (OIT) is a significant focus of treatment of food allergy. OIT appears to be effective in inducing desensitization, however, patients receiving OIT frequently developmild/moderate symptoms during the therapy. It has not been clearly established whether the clinical tolerance induced by OIT resembles natural tolerance. According to our data, the efficacy of OIT is different among food antigens, and it is comparatively difficult to achieve the clinical tolerance in milk OIT. Moreover, the definitive evidence of efficacy and safety with long-term therapy is limited. Further studies need to be offered to patients in clinical practice. Recently, novel treatments for food allergy, sublingual and epicutaneous immunotherapy, and combination treatment with an anti-IgE monoclonal antibody (omalizumab), have been examined in some studies. OIT combined with omalizumab increased the threshold doses of food without adverse reactions and may be of benefit in food allergy treatment. More studies are needed to demonstrate long-term safety and treatment benefits in a larger patient cohort.

Introduction

The prevalence rates of food allergy have increased in recent decades. The standard therapeutic approach to food allergy is the identification of causative foods and allergen avoidance [1] along with nutritional counseling. However, accidental exposure to causative food is quite common [2], and rapid medical treatment for accidental exposure is necessary. This leads to a poor quality of life for patients as well as their families because of the difficulty in avoiding the food to which they are allergic and the potential for unexpected sudden and life-threatening reactions [3].

The first report of oral immunotherapy (OIT) was described in 1908. One hundred years later, OIT to cow's milk revealed effective desensitization [4, 5].

KARGER

E-Mail karger@karger.com
www.karger.com/iaa

1018–2438/14/1641–0001$39.50/0

Correspondence to: Dr. Sakura Sato
Clinical Research Center for Allergy and Rheumatology, Sagamihara National Hospital
18-1, Sakuradai, Minamiku
Sagamihara-City, Kanagawa 252-0392 (Japan)
E-Mail s-satou@sagamihara-hosp.gr.jp

Table 1. Summary of OIT trials for food allergy

Food	Study (published year)	Subjects	Symptoms/therapy	Clinical outcomes 1	Clinical outcomes 2
Peanut	Jones et al. [8] (2009)	2–10 years OIT: 29	Initial day: 92% of the subjects At home: 3.7% of the OIT doses Adrenaline given 4 times for OIT	OIT: threshold dose ↑	Desensitization: 69% Dropout: 25%
	Blumchen et al. [10] (2010)	3–14 years OIT: 23	Rush phase: 7.9% of the OIT doses At home: 2.6% of the OIT doses No adrenaline given	OIT: threshold dose ↑	Desensitization: 61% Dropout: 35%
	Varshney et al. [17] (2011)	2–10 years OIT: 19 Control: 9	Initial day: 47% of the subjects At home: no data Adrenaline given 2 times for OIT	OIT: threshold dose ↑ Control: no change	Desensitization: 84% Dropout: 16%
Milk	Longo et al. [12] (2008)	5–17 years OIT: 30 Control: 30	Rush phase: 100% of the subjects At home: 57% of the subjects Adrenaline given 4 times for OIT	OIT: threshold dose ↑ Control: no change	Desensitization: 36% Dropout: 10%
	Skripak et al. [6] (2008)	6–17 years OIT: 13 Control: 7	45.4% of the OIT doses Adrenaline given 4 times for OIT	OIT: threshold dose ↑ Control: no change	Desensitization: 46% Dropout: 8%
	Pajno et al. [16] (2010)	4–13 years OIT: 15 Control: 15	80% of the subjects Adrenaline given 2 times for OIT	OIT: threshold dose ↑ Control: no change	Desensitization: 67% Dropout: 10%
Egg	Burks et al. [15] (2012)	5–11 years OIT: 40 Control: 15	Initial day: 27.4% of the OIT doses At home: 24.2% of the OIT doses No adrenaline given	OIT: threshold dose ↑ Control: no change	Desensitization: 55% Tolerance: 28% Dropout: 13%

These early reports led researchers to pursue OIT as a promising approach to treat food allergy. Recently, OIT has been investigated as a novel therapeutic approach for food allergy [6–14], and numerous clinical trials, including randomized controlled trials, have been completed. In this review, we will summarize the clinical trials of OIT and the progress in developing OIT for food allergy management.

Clinical Trials of OIT

The OIT method generally includes an initial rapid dose escalation phase, followed by a slower buildup phase to reach the maintenance dose. Treatment effectiveness is evaluated by an oral food challenge (OFC) following allergen avoidance for a certain period of time. Many studies have shown that the main outcome of OIT is desensitization and that allergen exposure continuously increases the threshold of clinical reactivity to food, although allergic reactions, mainly mild to moderate, occur during OIT [6, 7, 10, 12, 13, 15] (table 1). On the other hand, it is unknown whether clinical tolerance, which is defined as the ability to consume a food without having an allergic reaction, induced by OIT resembles the natural tolerance that has spontaneously arisen for food allergy patients.

Efficacy of OIT

Open-label pilot studies show that OIT increases the threshold of reactivity to causative food. Jones et al. [8] reported a study of peanut OIT in 29 subjects with peanut allergy. After therapy, 27 of the 29 subjects (93%) were able to ingest 3.9 g of peanut protein, whereas the remaining 2 subjects stopped at doses lower or equal to 2.1 g of peanut protein. Another peanut OIT study that enrolled 23 patients with peanut allergy provided similar results: 14 patients were fully desensitized, tolerating a peanut dose of 0.5–2 g, while 1 patient was partially desensitized. The remaining 8 patients dropped out of the study due to adverse reactions and compliance issues [10].

Several controlled studies involved patients with peanut, milk and egg allergy. These studies found significant differences between those who underwent OIT and those who were on an elimination diet [6, 12, 16]. Longo et al.

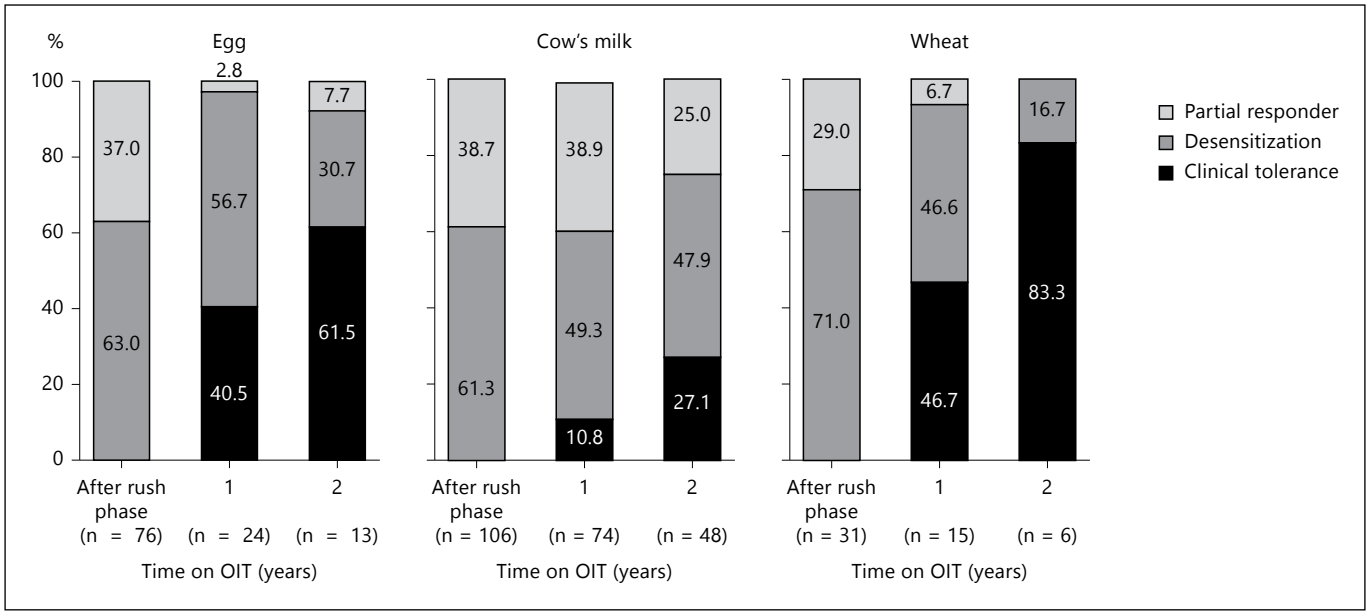

Fig. 1. Efficacy of OIT at the 2-year follow-up. Black boxes show 'clinical tolerance' that passed OFC after a 2-week allergen avoidance at the end of therapy. Dark gray boxes represent 'desensitization,' where allergen exposure continuously increases the threshold of clinical reactivity to the food. Light gray boxes demonstrate 'partial responders' who cannot achieve the maintenance dose.

[12] enrolled 60 patients with severe milk allergy with milk-specific IgE levels >85 kUA/l. One group underwent OIT to cow's milk; another group was kept on a milk-free diet (control group). After 1 year, 11 (36%) of 30 children in the OIT group were successfully desensitized (daily intake of ≥150 ml), 16 (54%) were partially desensitized (daily intake of 5–150 ml), and 3 (10%) could not complete the protocol because of allergic side effects. None of the subjects in the control group could tolerate 5 ml of cow's milk. Another peanut OIT multicenter study demonstrated that 16 (87%) of the 19 patients in the OIT group were desensitized, whereas placebo-treated patients could not ingest 5 g of peanuts [17].

More recently, the results from a double-blind, randomized, placebo-controlled study of OIT in 55 children with egg allergy were published [15]. After 10 months of therapy, none of the children in the placebo group and 55% of those who received OIT passed the OFC and were considered to be desensitized. Twenty-two months after the therapy, 75% of children in the OIT group were desensitized. Furthermore, after a 2-month complete egg avoidance, in the OIT group, 28% (11 of 40 children) passed the OFC at 24 months and were considered to have sustained unresponsiveness to the allergen. At 30 and 36 months, all children who had passed the OFC at 24 months were consuming egg without any problems [15].

These studies mostly excluded patients with food-induced anaphylaxis. However, these patients need effective interventions to avoid life-threatening accidents. Since 2008, we have been performing OIT for patients with egg, cow's milk and wheat anaphylaxis [18]. We enrolled 227 patients with food-induced anaphylaxis defined by double-blind, placebo-controlled, food challenge (DBPCFC). Our OIT protocol consists of three steps: (1) an initial buildup phase in the hospital; (2) a slow buildup phase at home, and (3) a maintenance phase. The patients undergo OFC after 2 weeks of allergen avoidance to confirm clinical tolerance. Fifteen patients withdrew from the study early because of allergic side effects or difficulty with the food intake. After 2 years, 92.2% of the patients receiving egg OIT (daily intake of 1 heated whole egg), 75.0% of the milk OIT patients (daily intake of 200 ml milk), and 100% of the wheat OIT patients (daily intake of 5.2 g wheat powder) were successfully desensitized (fig. 1). Moreover, the percentages of patients who passed OFC at the end of the therapy were 61.5% for egg OIT, 27.1% for milk OIT and 83.3% for wheat OIT; these patients might achieve clinical tolerance. Our data suggest that the efficacy of OIT is different among food antigens, and clinical tolerance is difficult to achieve in milk OIT patients.

Safety of OIT

The issue of patient safety is critical for OIT to be successful. Adverse reactions were frequent with OIT but mainly mild to moderate; severe adverse reactions requiring adrenaline injection were less common [6, 7, 10, 12, 13, 15] (table 1). The majority of these reactions occurred during the dose escalation phase in hospital, but, importantly, reactions to a previously tolerated dose of OIT during home dosing were common [19, 20]. Additionally, there have also been reports of eosinophilic gastrointestinal disorders developing in patients with OIT [21].

The overall risk associated with the allergen exposure varies with the population characteristics of the children enrolled. Unfortunately, most studies excluded patients with a history of severe reactions or anaphylaxis. In case of severe cow's milk allergy, the patients reported by Longo et al. [12] experienced more adverse reactions than those observed in other studies. In our trial of OIT patients with food-induced anaphylaxis, concerning the frequency of moderate and severe reactions, milk OIT patients showed the highest rate, followed by egg and wheat OIT patients. The patients requiring adrenaline injection were at 0.4% of the total OIT dose at home. Further OIT trials with severe food-induced anaphylaxis are needed to investigate the safety of OIT.

Patients with food allergy are at risk of an allergic reaction even on an elimination diet because of accidental exposure and with the rise in the consumption of processed food. Although OIT was associated with an increased risk of allergic reactions requiring adrenaline injection or systemic corticosteroids compared to those on an elimination diet in a systematic review of cow's milk OIT [22], its review reveals that those studies had a small number of patients enrolled. Therefore, it might be necessary to compare the risk of treatment with OIT and its side effects with an elimination diet.

The most common triggers for reactions to a previously tolerated dose are infection and exercise [6, 20, 23]. In food-allergic patients, viral or bacterial infections are generally known to affect symptom severity, especially in case of gastrointestinal infections. Exercise within 2 h after dosing, taking a dose on an empty stomach, poorly controlled bronchial asthma [20] and pollen allergy [23] are important triggers for a lower threshold reaction to OIT. Other factors may be associated with increased reactions to allergen, nonsteroidal anti-inflammatory drugs [24], physical exertion after dosing and dosing during menses [20]. Therefore, patients should be regularly monitored by an experienced allergist in the home-dosing phase, in case a previously tolerated dose causes a reaction when the immune system is compromised.

Issues of OIT for Clinical Practice

The results of previous studies indicate that OIT for food allergy is effective in increasing the amount of food tolerated in ≥50% of treated patients [6, 8, 10, 12, 15, 16]. However, many patients continue to be resistant to desensitization or achieve only partial desensitization. Additionally, numerous unanswered questions surrounding OIT remain, such as the increased risk of allergic reactions to OIT compared with food elimination and issues related to the treatment protocol, patient selection, management after desensitization, allocation of clinical resources and costs.

Currently, OIT protocols use different dosing schedules and varying durations of therapy. The optimal dose and length of therapy is also unclear. Previous studies on OIT have used a variety of doses [6, 13, 16, 25] and protocols are heterogeneous, making comparisons among them difficult. In 2012, Keet et al. [11] demonstrated that sublingual immunotherapy (SLIT) followed by OIT was much more effective for desensitization than SLIT alone. They also examined 2 OIT maintenance doses (1,000 vs. 2,000 mg), and no significant difference in either the overall rate of reaction or efficacy between these regimens was found. The results of the studies cited above point to the need for more studies with longer intervention periods and larger numbers of patients to resolve these questions.

How long would it take before the lack of a continued allergen intake would result in a loss of desensitization? Previous studies suggest that desensitization by OIT does not quickly lead to tolerance. Therefore, it is possible that a longer period of daily maintenance treatment may be required for most patients to develop tolerance or it may at least be similar to the maintenance period for inhaled-allergen subcutaneous immunotherapy.

Moreover, even in those who passed the OFC without receiving therapy, it is not yet clear whether they can be considered to have permanent tolerance or if they instead have transient desensitization. Desensitization and tolerance must be addressed. Desensitization is defined as 'a change in the threshold dose of an ingested food allergen necessary to cause allergic reactions' that can be short term or prolonged with ongoing therapy [26]. On the other hand, tolerance is defined as a permanent loss of reactivity correlated with the ability to ingest food without symptoms and without ongoing therapy [27]. There are little data available on whether OIT for food allergy in-

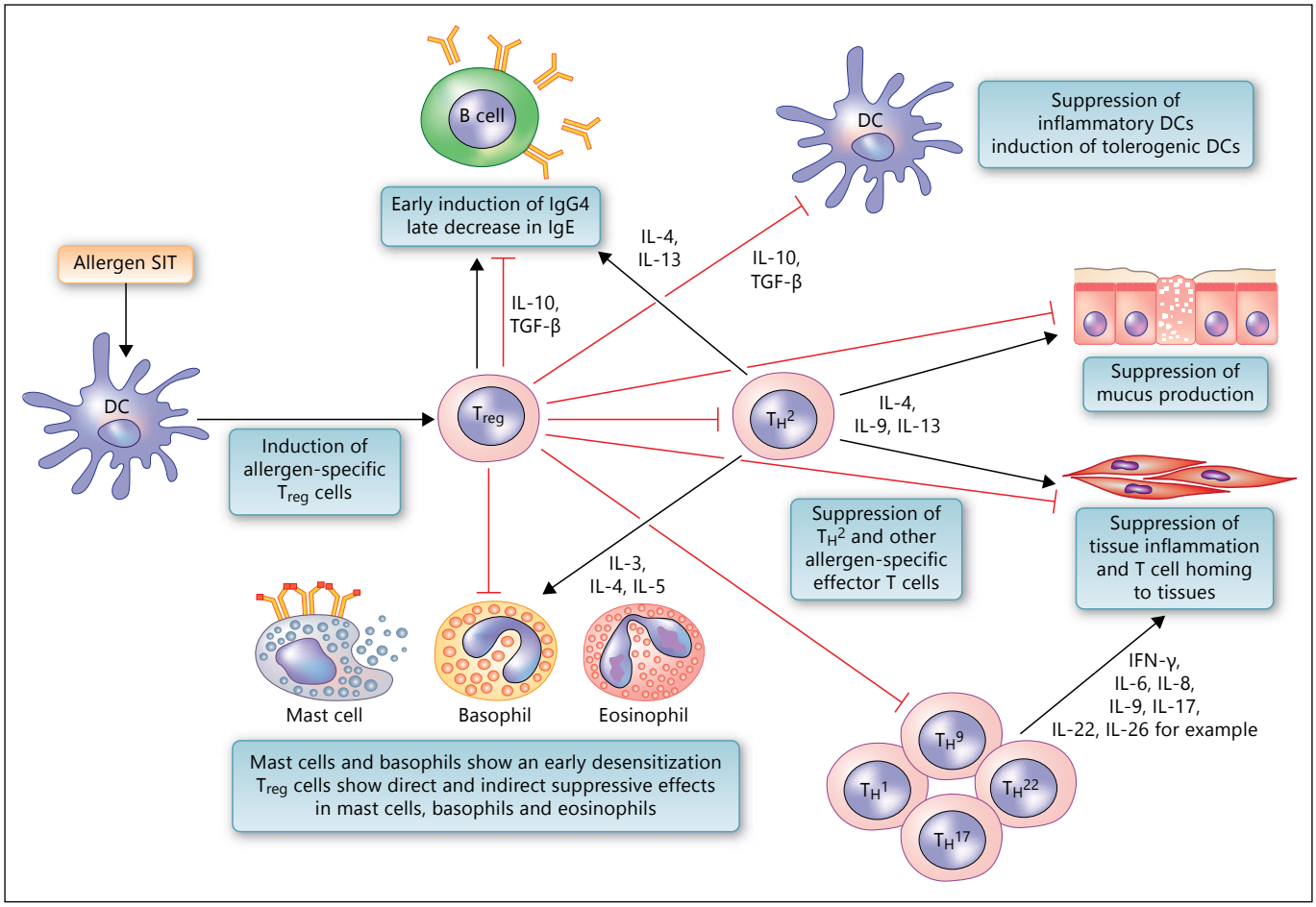

Fig. 2. Mechanisms of immunotherapy. DC = Dendritic cell.

duces permanent tolerance or if the effects represent transient desensitization. Many patients fail desensitization after stopping OIT according to Buchanan et al. [7] and Blumchen et al. [10]. In a recently published study by Keet et al. [11], 6 of the 15 subjects who passed a full milk challenge after 60 weeks of maintenance lost desensitization within 6 weeks after 1 week off therapy. Therefore, desensitization induced by OIT appeared to have failed after a short time. Although it seems likely that the state of desensitization requires ongoing exposure to be maintained, there are no answers regarding how much or how often allergen patients should ingest foods they were previously allergic to.

OIT is a promising therapy for food allergy, however, we remain at a state of equipoise with many unanswered questions to be studied. More studies are needed to address these issues in order to be able to determine whether OIT is appropriate for clinical practice.

Mechanisms and Immunologic Changes with OIT

OIT has been shown to modulate allergen-specific immune responses and to induce desensitization, however, the precise mechanisms of OIT remain uncertain. Immunologic responses to OIT in antigen-specific IgE and IgG4, mast cells, basophils and T cells mirror those seen with allergen immunotherapy for inhalant allergens and seem to be similar to the natural development of tolerance to food allergens [28, 29] (fig. 2).

OIT is most commonly associated with a reduction in antigen-specific IgE and an increase in antigen-specific IgG4. Jones et al. [8] reported that antigen-specific IgE levels in patients receiving OIT tended to increase early in the dose escalation phase and subsequently decrease compared with baseline values at 12 and 18 months. Then, for all subsequent time points, peanut-specific IgE levels tended to significantly decrease. A

Table 2. Immunologic responses to OIT

	Factors	Immunologic changes
Humoral changes	IgE	Specific IgE ↑ Specific IgE ↓
	IgG	Specific IgG ↑ Specific IgG returned to baseline level
	IgG4	Specific IgG4 ↑ Specific IgG4 increase throughout the OIT
Cellular changes	Mast cells	Skin prick test: wheal size to OIT allergen ↓
	Basophils	CD63 ↓ CD203c ↓ Spontaneous HR ↓ HR: no change
	Lymphocytes and PBMCs	Stimulated release of IL-2, IL-4, IL-5, IL-13 ↓ Stimulated release of IL-10, TGF-β, TNF-α ↑ FoxP3+ T cell ↑ Gene expression of apoptotic pathways ↓

HR = Histamine release; PBMC = peripheral blood mononuclear cells.

significant increase in specific IgG levels started 3 months after therapy initiation, remained high until 24 months and gradually returned to baseline by 33 months. On the other hand, specific IgG4 levels increased initially (with a statistically significant difference at 3 months) and remained elevated until the end of the study. Although an increase in antigen-specific IgG4 levels has been universally reported [7, 10, 15, 30], some studies reported no change in antigen-specific IgE levels during OIT [6, 7, 15, 16]. These changes in antigen-specific immunoglobulins were seen only in patients receiving OIT; therefore, the effect of OIT on antigen-specific immunoglobulins seems to occur in an allergen-specific manner [30].

Suppression of the effector cells is a predominant mechanism through which immunotherapy might function (table 2). Skin prick test reactivity showed a significant decrease beginning after several months and remained decreased throughout the 3-year follow-up [8]. Additionally, in patients on egg OIT, wheal size on skin prick testing was decreased compared to placebo-treated patients although there were no differences in egg-specific IgE levels between the two groups studied by Burks et al. [15]. They also reported that basophil activation decreased with OIT and that reduced basophil activation was associated with clinical desensitization. Some early studies reported that OIT induced basophil suppression at approximately 4–6 months [8, 31]. Therefore, effector cell suppression is a predominant mechanism through which OIT may be effective.

OIT-induced changes in cytokine responses have also been reported. Most studies reported reduced T_H2 and increased regulatory T cells (T_{reg}; table 2). Blumchen et al. [10] reported that peanut OIT was associated with reduced peanut-induced T_H2 cytokine production (IL-4 and IL-5). In contrast, Jones et al. [8] reported increased IL-5 and TNF-α production in patients who underwent peanut OIT. T_{reg} cell numbers were reported to increase with OIT (table 2). Jones et al. [8] reported FoxP3-expressing T_{reg} cells increased after OIT, returning to baseline levels by 20 months in peanut-stimulated cells [8].

Future Treatment for Food Allergy

Current OIT protocols are associated with frequent adverse reactions, the necessity of providing treatment for longer periods, and the failure of some patients to respond to the treatment. Therefore, additional therapeutic approaches to food allergy should be examined to assess whether the therapy can induce tolerance and to assess its safety (table 3).

Table 3. Future treatment of food allergy

Treatment	Allergen	Efficacy	Study (published year)
SLIT	Hazelnut	45% of the subjects reached 20 g after 8–12 weeks of study	Enrique et al. [32] (2005)
	Peanut	70% of 20 subjects were able to increase the threshold doses after 44 weeks of therapy	Fleischer et al. [33] (2013)
SLIT + OIT	Milk	70% of 20 subjects were able to pass the 8-gram oral challenge after 80 weeks of therapy	Keet et al. [11] (2012)
OIT + omalizumab	Milk	9 of 11 subjects reached 2,000 mg, passed the oral challenge on week 24 of the study	Nadeau et al. [36] (2012)
EPIT	Milk	90% of 10 subjects tended to increase the threshold doses at follow-up oral challenge (day 90)	Dupont et al. [37] (2010)

Sublingual Immunotherapy

In SLIT, doses that are quite small and lower than OIT doses are placed under the tongue of the patient. In several previous studies, it was demonstrated that SLIT with hazelnut, milk and peanut can increase the threshold of tolerated food allergens [11, 32, 33], and that adverse reactions were mostly mild enough to omit oral antihistamine administration. However, an important issue with the use of SLIT is the limited maximum dose that can be used sublingually. Keet et al. [11] attempted to directly compare the efficacy of SLIT and OIT in patients with cow's milk allergy. This study involved 30 randomized children with milk allergy receiving SLIT alone or SLIT followed by OIT. After an initial SLIT escalation, patients were randomized to continue either SLIT only or to begin OIT at two different maintenance doses. Sixty weeks later, only 1 patient in the SLIT group passed the OFC with 8 g of milk, compared to 6 in the lower-dose OIT group and 8 in the higher-dose OIT groups. Systemic reactions were more common during OIT than SLIT. In patients with peanut allergy treated with either peanut OIT or SLIT, OIT was also more efficacious than SLIT [34]. These results showed that OIT is more effective than SLIT alone in achieving desensitization. Combination therapy with SLIT and OIT may benefit from the safety of SLIT and the potential of achieving higher food doses with OIT.

Anti-IgE Monoclonal Antibodies (Omalizumab) for Food Allergy

Omalizumab, an anti-IgE monoclonal antibody, is a recombinant humanized monoclonal IgE-blocking antibody. It acts by decreasing or preventing allergic responses triggered by IgE molecules. Adjunctive administration of recombinant monoclonal anti-IgE therapy may be a promising strategy to address some of the safety concerns associated with OIT [35, 36].

Nadeau et al. [36] conducted a phase I pilot study by combining omalizumab treatment with milk OIT. After a 9-week pretreatment with omalizumab, OIT combined with omalizumab was followed by maintenance OIT without omalizumab, and, finally, a DBPCFC at week 24. Nine of 10 subjects achieved the target dose and passed the DBPCFC, and the frequency of adverse reactions, which were mostly mild, was 1.6%. Only 1 subject presented with rhinitis and generalized urticaria and responded to adrenaline at DBPCFC. The use of recombinant monoclonal anti-IgE therapy might be effective in reducing severe adverse reactions during the escalation phases of OIT. Randomized controlled trials of milk and peanut OIT are currently underway.

Epicutaneous Immunotherapy

Epicutaneous immunotherapy (EPIT) may be a novel approach to food allergy. EPIT, which involves the application of an allergen-loaded patch on intact skin, was shown to desensitize milk-allergic patients [37]. Patients in the active treatment group tolerated higher doses of milk on OFC during follow-up visits than patients in the placebo group. Adverse reactions consisted mostly of local skin reactions at the site of application and repeated episodes of diarrhea in 1 child, but any severe systemic reactions were not encountered. While this pilot study suggests that EPIT is safe and well tolerated, additional studies are required to assess its clinical efficacy.

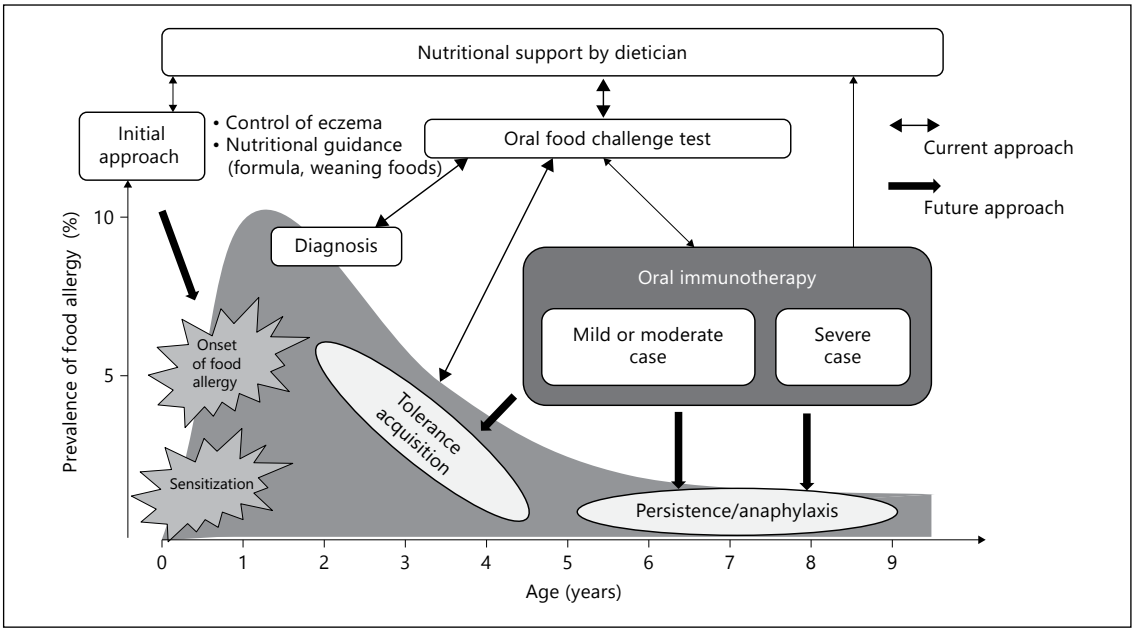

Fig. 3. New therapeutic approaches to food allergy.

Conclusion

OIT may offer a reasonable new intervention for persistent food allergy patients (fig. 3). OIT appears to be effective for food allergy and induces desensitization without major morbidity or mortality. However, the definitive evidence of efficacy and safety with long-term therapy is limited, and, in current protocols, entry criteria, and treatment and maintenance dosages during the optimal follow-up period await to be standardized. Currently, OIT cannot be offered to patients in clinical practice. Some novel treatment, particularly the combination of OIT with omalizumab, shows that patients can increase food tolerance without symptoms. The efficacy of OIT remains to be fully assessed in studies in larger patient cohorts.

Acknowledgments

We appreciate Ms. Noriko Hayashi, Ms. Miho Hasegawa, Ms. Chizuko Sugizaki and all of our coworkers. The study was supported by Health and Labor Sciences Research Grants for the Research on Allergic Diseases and Immunology from the Ministry of Health, Labor and Welfare (Japan).

References

1 Sampson HA: Food allergy. Part 2: diagnosis and management. J Allergy Clin Immunol 1999;103:981–989.
2 Sicherer SH, Furlong TJ, Munoz-Furlong A, Burks AW, Sampson HA: A voluntary registry for peanut and tree nut allergy: characteristics of the first 5149 registrants. J Allergy Clin Immunol 2001;108:128–132.
3 Cohen BL, Noone S, Munoz-Furlong A, Sicherer SH: Development of a questionnaire to measure quality of life in families with a child with food allergy. J Allergy Clin Immunol 2004;114:1159–1163.
4 Permaul P, Stutius LM, Sheehan WJ, Rangsithienchai P, Walter JE, Twarog FJ, et al: Sesame allergy: role of specific IgE and skin prick testing in predicting food challenge results. J Allergy Clin Immunol 2009;123:S24.
5 Zavalkoff S, Kagan R, Joseph L, St-Pierre Y, Clarke A: The value of sesame-specific IgE levels in predicting sesame allergy. J Allergy Clin Immunol 2008;121:1508–1510.
6 Skripak JM, Nash SD, Rowley H, Brereton NH, Oh S, Hamilton RG, et al: A randomized, double-blind, placebo-controlled study of milk oral immunotherapy for cow's milk allergy. J Allergy Clin Immunol 2008;122:1154–1160.
7 Buchanan AD, Green TD, Jones SM, Scurlock AM, Christie L, Althage KA, et al: Egg oral immunotherapy in nonanaphylactic children with egg allergy. J Allergy Clin Immunol 2007;119:199–205.
8 Jones SM, Pons L, Roberts JL, Scurlock AM, Perry TT, Kulis M, et al: Clinical efficacy and immune regulation with peanut oral immunotherapy. J Allergy Clin Immunol 2009;124:292.e97–300.e97.
9 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;59:980–987.

10 Blumchen K, Ulbricht H, Staden U, Dobberstein K, Beschorner J, de Oliveira LC, et al: Oral peanut immunotherapy in children with peanut anaphylaxis. J Allergy Clin Immunol 2010;126:83.e1–91.e1.

11 Keet CA, Frischmeyer-Guerrerio PA, Thyagarajan A, Schroeder JT, Hamilton RG, Boden S, et al: The safety and efficacy of sublingual and oral immunotherapy for milk allergy. J Allergy Clin Immunol 2012;129:448.e5–455.e5.

12 Longo G, Barbi E, Berti I, Meneghetti R, Pittalis A, Ronfani L, et al: Specific oral tolerance induction in children with very severe cow's milk-induced reactions. J Allergy Clin Immunol 2008;121:343–347.

13 Staden U, Blumchen K, Blankenstein N, Dannenberg N, Ulbricht H, Dobberstein K, et al: Rush oral immunotherapy in children with persistent cow's milk allergy. J Allergy Clin Immunol 2008;122:418–419.

14 Yu GP, Weldon B, Neale-May S, Nadeau KC: The safety of peanut oral immunotherapy in peanut-allergic subjects in a single-center trial. Int Arch Allergy Immunol 2012;159:179–182.

15 Burks AW, Jones SM, Wood RA, Fleischer DM, Sicherer SH, Lindblad RW, et al: Oral immunotherapy for treatment of egg allergy in children. N Engl J Med 2012;367:233–243.

16 Pajno GB, Caminiti L, Ruggeri P, De Luca R, Vita D, La Rosa M, 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 2010;105:376–381.

17 Varshney P, Jones SM, Scurlock AM, Perry TT, Kemper A, Steele P, et al: A randomized controlled study of peanut oral immunotherapy: clinical desensitization and modulation of the allergic response. J Allergy Clin Immunol 2011;127:654–660.

18 Ebisawa M, Sato S, Utsunomiya T, Hayashi N, Imai T, Yanagida T: Rush oral immunotherapy for the treatment of hen's egg- and cow's milk-induced anaphylaxis; in Marone G, Triggiani M, Genovese A (eds): Translational Science: From Basic to Clinical Immunology and Allergy. Pisa, Pacini, 2012, pp 359–364.

19 Hofmann AM, Scurlock AM, Jones SM, Palmer KP, Lokhnygina Y, Steele PH, et al: Safety of a peanut oral immunotherapy protocol in children with peanut allergy. J Allergy Clin Immunol 2009;124:286.e6–291.e6.

20 Varshney P, Steele PH, Vickery BP, Bird JA, Thyagarajan A, Scurlock AM, et al: Adverse reactions during peanut oral immunotherapy home dosing. J Allergy Clin Immunol 2009;124:1351–1352.

21 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;129:1155–1157.

22 Brozek JL, Terracciano L, Hsu J, Kreis J, Compalati E, Santesso N, et al: Oral immunotherapy for IgE-mediated cow's milk allergy: a systematic review and meta-analysis. Clin Exp Allergy 2011;42:363–374.

23 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;62:1261–1269.

24 Harada S, Horikawa T, Ashida M, Kamo T, Nishioka E, Ichihashi M: Aspirin enhances the induction of type I allergic symptoms when combined with food and exercise in patients with food-dependent exercise-induced anaphylaxis. Br J Dermatol 2001;145:336–339.

25 Patriarca G, Nucera E, Pollastrini E, Roncallo C, De Pasquale T, Lombardo C, et al: Oral specific desensitization in food-allergic children. Dig Dis Sci 2007;52:1662–1672.

26 Rolinck-Werninghaus C, Staden U, Mehl A, Hamelmann E, Beyer K, Niggemann B: Specific oral tolerance induction with food in children: transient or persistent effect on food allergy? Allergy 2005;60:1320–1322.

27 Scurlock AM, Vickery BP, Hourihane JO, Burks AW: Pediatric food allergy and mucosal tolerance. Mucosal Immunol 2010;3:345–354.

28 Akdis M, Akdis CA: Mechanisms of allergen-specific immunotherapy. J Allergy Clin Immunol 2007;119:780–791.

29 Akdis CA: Therapies for allergic inflammation: refining strategies to induce tolerance. Nat Med 2012;18:736–749.

30 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 2010;105:444–450.

31 Wanich N, Nowak-Wegrzyn A, Sampson HA, Shreffler WG: Allergen-specific basophil suppression associated with clinical tolerance in patients with milk allergy. J Allergy Clin Immunol 2009;123:789.e20–794.e20.

32 Enrique E, Pineda F, Malek T, Bartra J, Basagana M, Tella R, 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;116:1073–1079.

33 Fleischer DM, Burks AW, Vickery BP, Scurlock AM, Wood RA, Jones SM, et al: Sublingual immunotherapy for peanut allergy: a randomized, double-blind, placebo-controlled multicenter trial. J Allergy Clin Immunol 2013;131:119.e7–127.e7.

34 Chin SJ, Vickery BP, Kulis MD, Kim EH, Varshney P, Steele P, et al: Sublingual versus oral immunotherapy for peanut-allergic children: a retrospective comparison. J Allergy Clin Immunol 2013;132:476.e2–478.e2.

35 Lieberman JA, Chehade M: Use of omalizumab in the treatment of food allergy and anaphylaxis. Curr Allergy Asthma Rep 2013;13:78–84.

36 Nadeau KC, Kohli A, Iyengar S, DeKruyff RH, Umetsu DT: Oral immunotherapy and anti-IgE antibody-adjunctive treatment for food allergy. Immunol Allergy Clin North Am 2012;32:111–133.

37 Dupont C, Kalach N, Soulaines P, Legoue-Morillon S, Piloquet H, Benhamou PH: Cow's milk epicutaneous immunotherapy in children: a pilot trial of safety, acceptability, and impact on allergic reactivity. J Allergy Clin Immunol 2010;125:1165–1167.