Allergology International 65 (2016) 135–140

Contents lists available at ScienceDirect

Allergology International

journal homepage: http://www.elsevier.com/locate/alit

Review article

New approach for food allergy management using low-dose oral food challenges and low-dose oral immunotherapies

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ARTICLE INFO

Article history:
Received 27 August 2015
Received in revised form
13 October 2015
Accepted 27 October 2015
Available online 7 January 2016

Keywords:
Disease management
Food hypersensitivity
Immunoglobulin
Immunotherapy
Pediatrics

Abbreviations:

CM	Cow's milk
EAACI	European academy of allergy and clinical immunology
OFC	Oral food challenge
OIT	Oral immunotherapy
SPTs	Skin prick tests

ABSTRACT

A number of studies have suggested that a large subset of children (approximately 70%) who react to unheated milk or egg can tolerate extensively heated forms of these foods. A diet that includes baked milk or egg is well tolerated and appears to accelerate the development of regular milk or egg tolerance when compared with strict avoidance. However, the indications for an oral food challenge (OFC) using baked products are limited for patients with high specific IgE values or large skin prick test diameters. Oral immunotherapies (OITs) are becoming increasingly popular for the management of food allergies. However, the reported efficacy of OIT is not satisfactory, given the high frequency of symptoms and requirement for long-term therapy.

With food allergies, removing the need to eliminate a food that could be consumed in low doses could significantly improve quality of life. This review discusses the importance of an OFC and OIT that use low doses of causative foods as the target volumes. Utilizing an OFC or OIT with a low dose as the target volume could be a novel approach for accelerating the tolerance to causative foods.

Introduction

Cow's milk (CM), hen's egg, wheat, and peanut allergies are the most common food allergies in children.[1] Based on reports of the natural history of egg and milk allergies, children outgrow food allergies by the age of 6 years in approximately 50% of cases[2,3] and by the teenage years in approximately 75% of cases[4,5]; however, some children continue to have food allergies beyond their teenage years.

The 'Learning Early about Peanut Allergy' (LEAP) study revealed that the early introduction of peanuts significantly decreased the incidence of peanut allergy and modulated the immune response to peanuts among children at high risk for this allergy.[6] In CM and eggs, the temperature and duration, in addition to the presence of wheat, modulate the effect of heat on protein allergenicity.[7] Numerous studies have indicated that a large subset of children who react to unheated milk or egg can tolerate extensively heated forms of these foods,[8–11] with 70% of CM- or egg-allergic children able to tolerate baked milk or egg.[11] Furthermore, a diet that includes baked milk and eggs is well tolerated[7] and appears to accelerate the development of regular milk and egg tolerance when compared with strict avoidance.[12,13] These reports indicate that around 80% of patients allergic to milk or egg are able to tolerate baked milk or egg products.

An oral food challenge (OFC) is usually performed to determine whether a child has outgrown a food allergy. However, OFC tests can be hazardous for patients with severe allergy and should be avoided if the results of skin prick tests (SPTs) with egg white extract are >5 mm or >11 mm in children aged <2 years or ≥2 years, respectively, or if heated egg allergy is diagnosed.[14] The challenge food for baked milk contains 0.5–1.3 g CM protein (equivalent to 15–40 mL CM),[8, 15–17] and children who react to baked milk should avoid CM completely.[17] In one study, children with a casein SPT > 15 mm, casein-specific IgE > 10.3 kU/L, or milk-

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Peer review under responsibility of Japanese Society of Allergology.

http://dx.doi.org/10.1016/j.alit.2015.10.010

specific IgE > 20.6 kU/L did not pass the baked milk challenge.[15] Therefore, the indication for an OFC for baked products is limited to patients with a high specific IgE value or large SPT diameter. Based on the specific cause of the food allergy, avoidance of the allergen is the only effective therapeutic option for these cases.

Other treatment options currently being investigated in clinical trials include oral immunotherapy (OIT),[18–20] which is becoming increasingly popular to treat food allergies. The reported efficacy of OIT is not satisfactory because of the high frequency of symptoms and requirement for long-term therapy.[19–21] Therefore, treatment approaches with a higher level of safety are desired.

With food allergies, removing the need to eliminate a food that might be consumed in low doses could significantly improve quality of life. For example, 86.4% of patients with a positive heated milk OFC can safely tolerate 10 g of butter.[22] Therefore, this review discusses the importance of OFCs and OITs that use low doses of causative foods as the target volumes.

Low-dose oral food challenge

The important feature of the OFC used in our hospital is the use of multiple steps for each causative food (Table 1). Ordinarily, we start the OFC from step 1; however, with high-risk patients, such as patients with a high specific IgE level (Immuno CAP assay system), past history of severe anaphylactic reactions, or a low threshold volume for causative foods, we consider starting from step 0, which involves the low-dose OFC.[23,24] In this section, we introduce the low-dose OFC by retrospectively reviewing data for subjects with reactions to low doses of causative foods who underwent a low-dose OFC.

Patients' backgrounds

Of the 667 children who underwent a low-dose OFC for CM or wheat between July 2012 and December 2014, those with missing clinical (n = 66) or laboratory data (n = 198), such as casein for milk or ω-5 gliadin for wheat, were excluded. Therefore, the analyses included 403 subjects: 217 subjects for CM (median age, 6.0 years; interquartile range, 3.8–9.3 years) and 186 subjects for wheat (median age, 6.8 years; interquartile range, 3.3–9.3 years).

For the children who underwent the CM OFC, the median milk-specific IgE level was 22.1 kUA/L (interquartile range, 6.0–59.8 kUA/L), and the median casein-specific IgE level was 20.4 kUA/L (interquartile range, 5.1–58.7 kUA/L). For the children who underwent the wheat OFC, the median wheat-specific IgE level was 26.9 kUA/L (interquartile range, 3.4–62.9 kUA/L), and the median ω5-specific IgE level was 1.6 kUA/L (interquartile range, 0.4–6.4 kUA/L).

Table 1
Stepwise oral food challenge, with the amount of protein ingested for each challenge food.

Step	Egg	Cow's milk	Wheat	Peanuts
0	One boiled egg yolk (2 mg)	Pumpkin cake containing 3 mL heated milk (102 mg)	2 g udon noodles (52 mg)	0.5 g peanut (133 mg)
1	1/32 of a heated whole egg (194 mg)	Pumpkin cake containing 25 mL heated milk (850 mg)	15 g udon noodles (390 mg)	3 g peanut (795 mg)
2	1/2 of a heated whole egg (3100 mg)	48 g yogurt (1700 mg)	50 g udon noodles (1300 mg)	10 g peanut (2650 mg)
3	One scrambled egg (6200 mg)	200 mL cow's milk (6800 mg)	200 g udon noodles/1 slice white bread (5200 mg)	–

The amount of protein is provided in the parentheses.

Oral food challenge protocol

The OFC for CM or wheat included 3 mL heated CM (equivalent to 102 mg CM protein) or 2 g udon noodles (equivalent to 52 mg wheat protein), respectively (Supplementary Fig. 1).

The challenge food in the low-dose milk OFC was pumpkin cake containing CM, which was prepared by mixing 3 mL CM, 3 g pumpkin, 2 g sorghum bicolor, 1 g sugar, 0.02 g baking soda, and 1 mL water (Supplementary Fig. 1). The mixture was heated to 90 °C (core temperature) for 1.5 min in a 1000-W microwave. The challenge food in the low-dose wheat OFC was 2 g boiled udon noodles, which are a traditional Japanese food prepared by boiling a mixture of wheat flour, water, and salt for 1 min.

The OFC was performed using an open challenge method during hospitalization. We performed the low-dose OFC by administering the cake in 2 separate portions 1 h apart. The initial dose was one quarter of the low-dose OFC, and the second dose was the remaining three quarters. A positive OFC was defined as the occurrence of the moderate or severe objective symptoms or the subjective symptoms listed in Table 2, based on the grading of

Table 2
Grading of symptoms of Japanese anaphylaxis guideline.

	1 (mild)	2 (moderate)	3 (severe)
Skin	Localized urticaria, exanthema, wheal, pruritus	Generalized urticaria, exanthema, wheal, pruritus	–
	Swollen eyelid or lip	Swollen face	–
Gastrointestinal tract	Pruritus of the throat or oral cavity	Throat pain	–
	Mild abdominal pain	Moderate abdominal pain	Cramps
	Nausea, emesis, diarrhea	Recurrent emesis, diarrhea	Continuous emesis, loss of bowel control
Respiratory tract	Intermittent cough, nasal congestion, sneezing, rhinorrhea	Repetitive cough	Persistent cough, hoarseness, "barky" cough
	–	Chest tightness, mild wheezing	Apparent wheezing, dyspnea, cyanosis, saturation <92%, swallowing or speaking difficulties, throat tightness, respiratory arrest
Cardiovascular	–	Pale face, mild hypotension, tachycardia (increase >15 beats/min)	Hypotension, dysrhythmia, severe bradycardia, cardiac arrest
Neurological	Change in activity level, tiredness	"Light-headedness," feeling of "pending doom," somnolence	Confusion, loss of consciousness, incontinence

The severity score was based on the organ system that was most affected by the symptoms. Hypotension was defined as a systolic blood pressure of <70 mmHg (ages, 1 month to 1 year), <(70 mmHg + [2 × age]) (ages, 1–10 years), and <90 mmHg (>11 years). Mild hypotension was defined as systolic blood pressure of <80 mmHg (ages, 1 month to 1 year), <(80 mmHg + [2 × age]) (ages, 1–10 years), and <100 mmHg (>11 years). This definition was modified using the anaphylactic symptom grading of the European Academy of Allergology and Clinical Immunology guidelines.
Total severity scores were calculated as the sum of the grades for cardiovascular symptoms, respiratory symptoms, and the maximum grades for the remaining symptoms.

symptoms in the Japanese anaphylaxis guideline[25]: moderate urticaria, continuous cough, moderate or severe abdominal pain, vomiting, or diarrhea. If mild objective symptoms were observed, the subject was carefully monitored to detect any worsening of symptoms. If the mild symptoms disappeared within 30 min, the OFC was continued, following informed consent from the patients and their guardians. When necessary, the physicians selected appropriate treatment measures based on the European Academy of Allergy and Clinical Immunology (EAACI) food allergy and anaphylaxis guidelines, including fluid resuscitation, oxygenation, intravenous or oral antihistamines, intravenous steroids, inhaled β2 agonists, or intramuscular adrenaline.[26]

Results of the low-dose oral food challenges

The results are presented as the OFC positive rates and probability curves (Fig. 1). The positive rates were 58.1% for milk and 43.0% for wheat. The probabilities of failing the low-dose CM OFC with a milk-specific or casein-specific IgE level of 100 kU/L were 71.6% and 75.6%, respectively. The probabilities of failing the low-dose wheat OFC with a wheat-specific or ω-5 gliadin-specific IgE level of 100 kU/L were 63.6% and 90.9%, respectively.

In other words, although the specific IgE level is >100, the probability of a positive challenge is <95%. Therefore, even for high-risk patients, such as patients with a past history of anaphylactic reactions or a high specific IgE level, a low-dose OFC can be performed. We believe that the only exclusion criterion for a low-dose OFC is the recent occurrence of moderate to severe symptoms with low doses of causative foods. A specific IgE level indicative of a negative or positive predictive value >95% could not be calculated. In a similar report, the milk-specific IgE level indicative of a negative predictive value >95% was 17.8 kUA/L, and patients with low milk-specific IgE levels might be able to safely consume butter.[22]

Dose progression and follow-up after the low-dose oral food challenges

Subjects who passed the low-dose OFC were advised to consume a food containing 3 mL heated CM or 10 g butter (equivalent to 2.9 mL CM[22]) for CM allergy or 2 g boiled udon noodles for wheat allergy at home at least once a week. For CM allergy, 1–3 months after the OFC was passed, the CM dose was increased to 25 mL heated CM either during an OFC in our hospital or gradually at home.[23] Within 1 year after confirming the tolerance to the low-dose OFC, 45% (18/41) of patients were able to consume 25 mL heated CM. Regarding wheat, within 1 year after confirming the tolerance to 2 g boiled udon noodles, 56% (18/32) of patients were able to consume 15 g boiled udon noodles.[24] Only a few patients had symptoms at home, 9.8% of those with CM allergy and 3.1% of those with wheat allergy, and the symptoms were not severe in any of the cases.

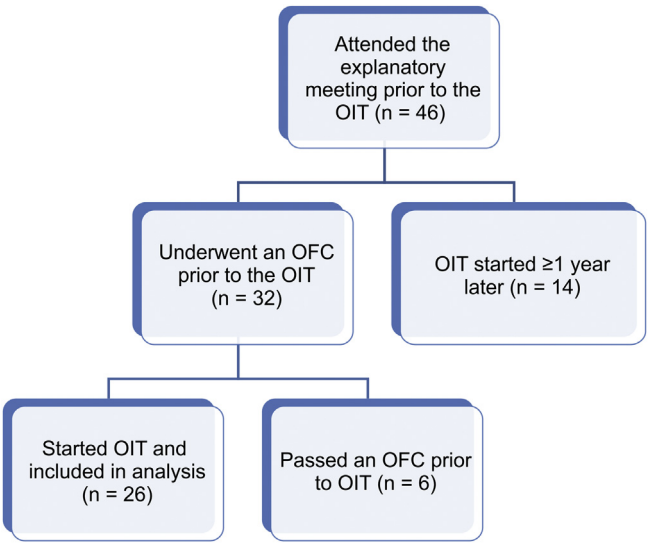

Fig. 2. Participation in the study of low-dose oral immunotherapy (OIT) using low-dose oral food challenges (OFCs) for milk, egg, wheat, and peanut.

Usefulness of the low-dose oral food challenge

The low-dose OFC seems to be useful for confirming tolerance to low doses of causative foods and improving the prognosis after 1 year. Including low doses of causative food in the diet of patients with a food allergy after a low-dose OFC might improve quality of life.

Introduction of low-dose oral immunotherapy

As already discussed, most, but not all, patients can eat low doses of causative foods. For cases who cannot, we conduct OIT with low doses as the target volume for causative foods. To the best of our knowledge, the only publication regarding low target volume immunotherapy for food allergy discusses sublingual

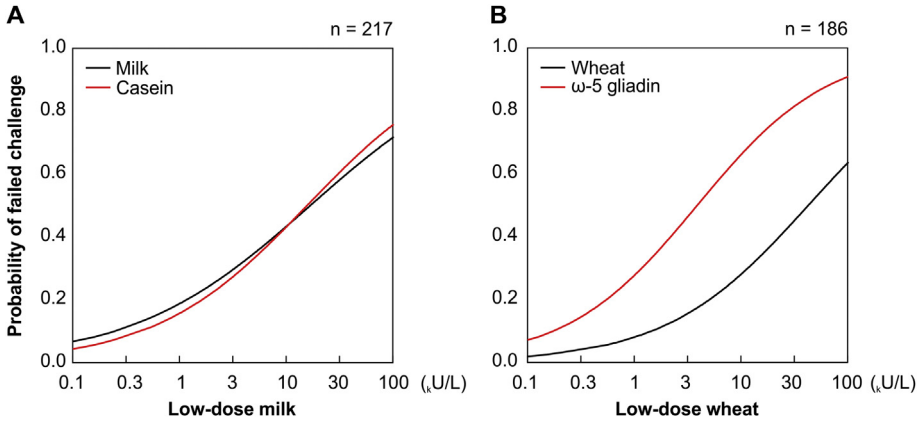

Fig. 1. Fitted predicted probability curves for the outcome of an oral food challenge at a given IgE level of **A)** milk and casein for 3 mL heated milk and **B)** wheat and ω-5 gliadin for 2 g boiled udon noodles. The positive rates were 58% for milk and 43% for wheat.

immunotherapy[27]; although sublingual immunotherapy is safer than OIT, it is less effective.[28,29]

In this section, we introduce low-dose OIT based on our single-center pilot study that was performed at Sagamihara National Hospital between January 2013 and March 2015 (UMIN000011202). We aimed to investigate the efficacy and safety of low-dose OIT (3 mL milk, 1/32 of a whole egg, 2 g boiled udon noodles, or 0.5 g peanut) using lower target volumes than what is conventionally used.

Patients' backgrounds

Of the 46 patients whose guardians attended an explanatory meeting prior to the OIT, OFCs using low doses of causative foods were performed with 32 patients; 6 negative cases were excluded, resulting in 26 cases being included in the analysis (Fig. 2).

A history of anaphylaxis was present in 80% (11/12) of the patients with CM allergy, 67% (4/6) of those with egg allergy, 100% (5/5) of those with wheat allergy, and 80% (4/5) of those with peanut allergy. The median milk-specific, egg white-specific, wheat-specific, and peanut-specific IgE levels were 39.4 kU/L, 44.1 kU/L, 151 kU/L, and 56.0 kU/L, respectively (Table 3).

Methods of introducing low-dose oral immunotherapy

The patient was admitted to the hospital for 5 days for build-up (Table 4). On the first day, an open OFC was conducted using foods masked by cocoa (milk, pumpkin cake containing 3 mL milk; egg, pumpkin cake containing 1/32 of a whole egg; wheat, pumpkin cake containing 52 mg wheat protein; and peanut, pumpkin cake containing 0.5 g peanut powder), and the occurrence of objective symptoms was confirmed. Oral administration of 10-mg loratadine commenced on the first night of admission. The same OFC was performed on the second day. On the third day, causative foods at half of the threshold of the accumulated volume of the OFC on the previous day were administered twice daily at 2-h intervals; if symptoms did not appear, double the volume was administered on the fourth day. If symptoms did appear, the same volume was administered on the fourth day. On the fifth day, an OFC was performed using a single administration of the volume that could be consumed on the fourth day without symptoms.

At home, the subjects were encouraged to drink or ingest causative foods once a day. The initial dose was the same dose that was safely consumed on the fifth day in hospital; then, the volume was gradually increased every 5 days up to a maximum target volume that was the same amount used in the first OFC. Once the target volume was reached, oral administration of loratadine was ceased. The subjects kept a diary to assess the presence or absence of symptoms.

Approximately 1 year later, the subjects stopped the daily intake of causative foods for two weeks, and an open low-dose OFC was performed. Tolerance for low doses of the causative food was defined as a negative result; with a negative result, a middle-dose OFC was performed on the next day with 25 mL milk, 1/2 of a whole egg, 15 g boiled udon noodles, or 3 g peanut. Tolerance for middle doses of the causative food was defined as a negative result with the middle-dose OFC. Desensitization was defined as being able to consume the low dose of the causative food without symptoms.

Table 4
Doses used in and location of the low-dose oral immunotherapy for milk, egg, wheat, or peanut.

Phase of the study	Location	Milk	Egg	Wheat	Peanut
Initial open OFC (Days1, 2)	Hospital	3 mL heated milk	1/32 of a heated whole egg	52 mg wheat	0.5 g peanut
Escalation (Days 3–5)		0.1–3 mL raw milk	1/128 to 1/32 of a heated whole egg	0.1–2 g udon noodles	0.04–0.5 g peanut
Build up	Home	0.1–3 mL raw milk	1/128 to 1/32 of a heated whole egg	0.1–2 g udon noodles	0.04–0.5 g peanut
Maintenance (Approximately 3 months)		3 mL raw milk	1/32 of a heated whole egg	2 g udon noodles	0.5 g peanut
Second open OFC after 2 weeks of elimination 1 year later	Hospital	3 mL heated milk	1/32 of a heated whole egg	52 mg of wheat	0.5 g of peanut
Open OFC (after passing the second OFC)		25 mL heated milk	1/2 of a heated whole egg	15 g udon noodles	3 g peanut

OFC, oral food challenge.
Low-dose oral immunotherapy comprises lower doses of the foods (3 mL milk, 1/32 of a whole egg, 2 g boiled udon noodles, or 0.5 g peanut) than what is conventionally used. Approximately 1 year later, the subjects stopped the daily intake of causative foods for two weeks, and an open low-dose OFC was performed. If this was negative, a middle-dose OFC was performed on the next day with 25 mL milk, 1/2 of a whole egg, 15 g boiled udon noodles, or 3 g peanut.

Results of the low-dose oral immunotherapy

The proportions of the subjects who were tolerant to low doses of the causative foods after 1 year were 60% (6/10) for milk, 83% (5/6) for egg, 80% (4/5) for wheat, and 100% (5/5) for peanut (Fig. 3). The proportions of the subjects who were tolerant to middle doses of the causative foods after 1 year were 40% (4/10) for milk, 50% (3/6) for egg, 20% (1/5) for wheat, and 100% (5/5) for peanut. Therefore, the rate of tolerance to the middle dose of wheat was lower than that of other foods.

Symptoms and treatment rates

We also compared the rates of symptoms and treatment (calculated per intake for one person) with the low-dose OIT to

Table 3
Baseline characteristics of the 26 participants undergoing low-dose oral immunotherapy for milk, egg, wheat, or peanut.

Characteristic	Milk (n = 10)	Egg (n = 6)	Wheat (n = 5)	Peanut (n = 5)
Age, years	8.5 (5.8–9.7)	9.4 (6.5–13.1)	7.3 (5.8–8.4)	8.4 (6.7–11.8)
Male, sex	6 (60)	2 (50.0)	2 (40)	5 (100)
Past history of anaphylaxis to milk	8 (80)	4 (67)	5 (100)	4 (80)
AD, current	5 (50)	1 (17)	1 (20)	2 (40)
BA, current	5 (50)	1 (17)	3 (60)	3 (60)
AR, current	5 (50)	4 (67)	2 (40)	3 (60)
Antigen-specific IgE level, Ua/mL	39.4 (1.7–278.0)	44.1 (5.4–210)	151 (4.5–399)	56.0 (17–328)
Threshold of the first challenge test, mg	30.6 (25.5–102)	86.8 (62–223.2)	52 (19.5–52)	132.5 (26.5–132.5)

Data are expressed as the median (25–75th percentile) or n (%).
AD, atopic dermatitis; BA, bronchial asthma; AR, allergic rhinitis.

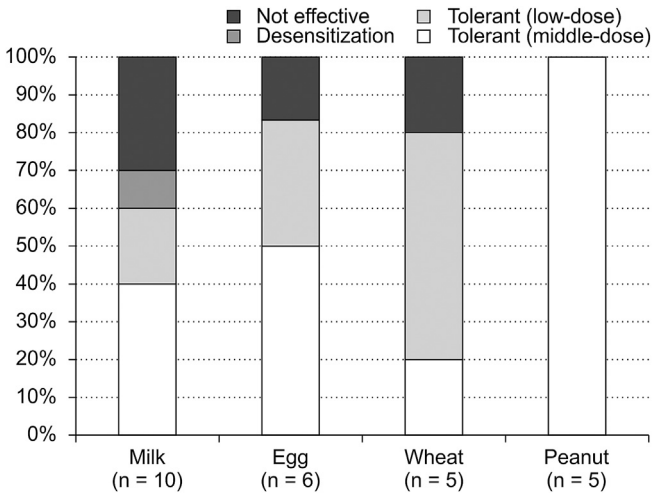

Fig. 3. Results of the second oral food challenge (OFC) for milk, egg, wheat, or peanut one year after the first OFC. Desensitization was defined as being able to consume a low dose of the causative food (3 mL milk, 1/32 of a whole egg, 2 g boiled udon noodle, or 0.5 g peanut) without symptoms. Low-dose tolerance was defined as a negative result in the low-dose OFC after 2 weeks of complete elimination of milk from the daily meals. Middle-dose tolerance was defined as a negative result in the middle-dose OFC (25 mL milk, 1/2 of a whole egg, 15 g boiled udon noodles, or 3 g peanut).

those with conventional rush OIT[19,30] at home after the first year (Table 5). The symptom rates were 15.5% with low-dose OIT and 15.0% with rush OIT; moderate or severe symptoms represented 1.6% and 2.3% of the symptoms with low-dose OIT and rush OIT, respectively ($p < 0.001$). The treatment rates were 2.7% and 4.3% with low-dose OIT and rush OIT, respectively ($p = 0.014$). Intramuscular adrenalin accounted for 0.04% and 0.13% of the treatments with low-dose OIT and rush OIT, respectively ($p = 0.035$). Adrenaline was used for only one patient who developed a cough after consuming 2.5 mL milk at home.

Usefulness of low-dose oral immunotherapy

The frequency of side effects affects quality of life after OIT.[31] In our study of low-dose OIT for high-risk patients with high antigen-specific IgE values or a history of past anaphylactic symptoms, the frequency of the induced symptoms was low compared with the frequency induced by conventional oral immunotherapy,[32] and the frequency of moderate to severe symptoms was also low and similar to that with sublingual immunotherapy.[26] This suggests that low-dose OIT might be a relatively safe treatment, likely owing to the fact that our OIT method did not encourage increasing the doses to more than the low dose level; this reduces the risk of symptoms during dose escalation, which some studies have reported as a risk factor for adverse reactions.[33,34] Although it was effective, baked milk oral immunotherapy in baked milk-reactive patients resulted in the need for intramuscular adrenalin in 3 of 15 patients during the process of increasing the threshold.[35]

Low-dose OIT might be a relatively safe and effective treatment method for food allergy patients with persistent and severe anaphylactic reactions. Continuing the intake of small amounts seems to be effective for tolerating larger amounts of causative foods. A prospective randomized control trial with a larger sample size is warranted to determine the safety and efficacy of low-dose OIT.

Table 5
Symptoms and treatments related with low-dose oral immunotherapy (OIT) or conventional rush OIT at home during the first year.

	Low-dose OIT (n = 26)	Rush OIT (n = 220)	p value
Rate of symptoms	15.5%	15.0%	0.430
Rate of moderate or severe symptoms	1.6%	2.3%	<0.001
Treatment rate	2.7%	4.3%	0.014
Rate of adrenaline use	0.04%	0.13%	0.035

Data are expressed as the mean rate. Fisher's exact tests were used for comparisons.

Conclusion

Utilizing an OFC or OIT with a low dose as the target volume could be a novel approach for accelerating the tolerance to causative foods and improving the quality of life of patients with food allergies.

Acknowledgments

We thank all of the pediatricians, nutritionists, and nurses at Sagamihara National Hospital who assisted with the patient recruitment and data collection. This study was supported by the Health and Labor Sciences Research Grants of the Research on Allergic disease and Immunology from the Ministry of Health, Labor, and Welfare in study design, data collection, analysis, and interpretation of data. Grant number is 201414009A. We would like to thank Editage (www.editage.jp) for English language editing.

The author (NY) received the JSA Best Presentation Award 2014 from the Japanese Society of Allergology for this work.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.alit.2015.10.010.

Conflicts of interest

ME received lecture fees from Pfizer. The rest of the authors have no conflict of interest.

Authors' contributions

NY performed the research, analyzed the data, and wrote the paper. YO analyzed the data. SS and ME contributed to the data analysis and the preparation and revision of the manuscript. All authors read and approved the final manuscript.

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