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Review article

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

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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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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.