REVIEW

Practical issues of oral immunotherapy in egg or milk allergy

Running title: Egg and milk oral immunotherapy

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Conflicts of interest
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ABSTRACT

Oral immunotherapy (OIT) has been recommended to reduce parental burden related to strict allergen avoidance as well as to induce desensitization and immune tolerance for patients with long-lasting allergies to hen’s eggs (HE) or cow’s milk (CM). OIT should be monitored by pediatric allergists specializing in OIT and oral food challenge tests to cope with allergic reactions. Although a previous history of anaphylaxis or multiple food allergy is not a contraindication to OIT, it is absolutely contraindicated if the patient has uncontrolled asthma, malignancy, active systemic autoimmune disorders, or diseases requiring treatment with beta-blockers. A variety of OIT protocols have been developed for better outcomes and safe up-dosing including adjunctive therapies with biologics. This review provides insights into the practical issues of various immunotherapy options in children with HE or CM allergies.

Key words: Egg allergy, Food allergy, Milk allergy, Oral food challenge, Oral immunotherapy

Key message

- OIT should be performed by specialized pediatricians with experience in oral food challenge tests and allergic reaction management.

- OIT involves an initial escalation and a build-up phase, during which food antigen intake is gradually increased. This is followed by a maintenance phase lasting several months to years.

- Patients may experience allergic reactions and psychological problems during OIT, and action plans should be in place to manage adverse reactions and subsequent OIT schedules.

- Adjunctive therapies such as biologics, antihistamines, and leukotriene receptor

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agonists may be used to improve the efficacy and safety of OIT.

- Contraindications for OIT include uncontrolled asthma, malignancy, active systemic autoimmune disorders, or diseases requiring beta-blockers.
**Introduction**

Food allergy (FA) is a rising public health problem in childhood, with a worldwide prevalence of approximately 3%-6%\(^1,2\). In Korean schoolchildren, the prevalence of immediate-type FA in 2015 was reported to be 3.2% in 6- to 7-year-olds, 4.5% in 9- to 10-year-olds, 4.0% in 12- to 13-year-olds, and 4.5% in 15- to 16-year-olds.\(^1\) Hen’s egg (HE) and cow’s milk (CM) are the most frequent causative food allergens in Korean children younger than 18 years.\(^1,3-5\) The public health burden of FA has become important, as it can cause major quality of life (QoL) impairments for patients and their families.\(^6,7\) Indeed, young patients and parents who have experienced anaphylaxis are more likely to develop psychiatric diseases such as posttraumatic stress disorder, anxiety, and depression.\(^8,9\) Previous studies reported that families of children with FAs spent additional direct and indirect household costs of up to $2,500 and $1,800 a year compared to families with healthy children.\(^6\)

Although strict allergen avoidance is the only way to prevent food-induced allergic reactions, it is difficult for caregivers to restrict eggs and milk from a variety of processed foods.\(^10\) Restriction of these protein sources in the diets of children and adolescents also has a negative effect on the health status of patients with these allergies.\(^2,11\) In our recent study, only half of the Korean children allergic to CM or egg white (EW) outgrow their allergies at 8.7 and 5.6 years of age, respectively.\(^12\) Given these difficulties, oral immunotherapy (OIT) has emerged as an active treatment option to induce desensitization and immune tolerance for patients with long-lasting allergies to HE or CM.\(^13\) This review highlights current knowledge and future perspectives on various immunotherapy strategies in children with IgE-mediated HE or CM allergies.

**Preparations for oral immunotherapy**
Recent guidelines have recommended OIT for children who have IgE-mediated FAs and place a high value on being able to eat offending foods under the supervision of a specialist from around 4 to 5 years of age. In order to safely and successfully conduct OIT, an accurate diagnosis of IgE-mediated FA through detecting specific IgE antibodies and oral food challenge (OFC) tests should precede OIT. It is also recommended to perform an OFC to determine the baseline threshold of offending foods, determine the degree of cooking required, and assess desensitization or sustained unresponsiveness (SU) after OIT. Although double-blind placebo-controlled OFC tests are the gold standard for the diagnosis of FAs, an open challenge test with a four- or six-dose protocol can be used in children to confirm FAs due to the low possibility of bias and psychological effects. The OFC dose can be set depending on the purpose, such as confirming FAs or determining the initial dose for OIT. Desensitization and SU were regarded when there was no reaction during OFC testing with a target dose after a build-up phase and after at least 2-4 weeks of avoidance following maintenance therapy, respectively.

OIT should be attended by specialized pediatricians who are well aware of this treatment option and have experience conducting OFC tests and dealing with allergic reactions. Prior to the beginning of OFC and OIT, informed consent should be obtained from the patient’s guardians after providing sufficient information on the process, potential outcomes, benefits, and risks of OIT. Hospitals should be equipped with drugs and facilities for possible symptoms associated with OFC tests or OIT. The individualized OIT schedule should be provided to the patient’s caregivers in clear and simple documents.

It is necessary to prepare protocols for visiting hospitals according to the situation of each country or center, as access to medical care and financial burden in the OIT process may differ from country to country. In addition, the types and cooking methods of food consumed
during OIT contribute to the effectiveness and adherence to the OIT protocol. For example, scotch pancakes and shepherd's pie, mainly eaten in the UK to treat CM allergies, are not familiar to Koreans. Boiled eggs, which are easy to prepare at home, may not be advantageous in inducing SU or oral tolerance. Although OIT with inpatient and outpatient management has been conducted at several hospitals in Korea, there is a large variance among OIT protocols. Therefore, as reported in other countries such as France, Canada, Spain, and Japan, evidence-based guidelines will be needed to perform OIT safely and effectively.

**Immunological changes during OIT**

As the amount of food consumed increases during OIT, allergen exposure leads to T helper 2 (Th2) and allergen-specific Th2 anergy as well as an increase in regulatory T (Tregs) and IL-10-producing CD4+ T cells, which results in reduced production of specific IgE and increased levels of allergen-specific IgA and IgG4. Circulating allergen-specific IgG neutralizes allergens, while IgG bound to the cell surface FcγRIIb induces inhibitory signaling with IgE and IgG crosslinking, preventing mast cell and basophil degranulation in desensitized patients. A decrease in wheal size in skin prick tests is found several months after OIT, which is related to basophil hyporesponsiveness. A recent study using single-cell RNA-Seq and paired T cell receptor α/β sequencing demonstrated that better OIT outcomes were associated with stronger suppression of Th2 module expression in Th2A-like cells. At the same time, there was an association between treatment failure and the expression of inflammatory gene signatures in Th1 and Th17 cells. Further studies are needed to elucidate the mechanism by which OIT affects the ability to reach SU at the cellular level.
Conventional oral immunotherapy

OIT consists of an initial escalation and a build-up phase in which food antigen intake is gradually increased until a target dose is reached. The build-up phase is followed by a maintenance phase in which the daily intake of food antigens is maintained for several months to years.\(^{13}\) Initial dose escalation is performed on days 1-3, beginning with an extremely small dose rapidly increasing (usually from 0.01 to 0.1 mg protein) and remaining at subthreshold levels to identify a safe dose.\(^{11,30,32}\) During the build-up phase, the increases in the allergens, according to various protocols, are conducted under a physician's supervision by up to 25%-100% every 1 to 2 weeks until the target maintenance dose (300 to 4,000 mg protein) is achieved.\(^{23,32,33}\) Burks et al. first evaluated OIT using EW powder for the treatment of children with HE allergy in a double-blind, randomized, placebo-controlled study.\(^{30}\) After 10 months, none of the children in the control group and 55% in the OIT group passed the OFC; after 22 months, 75% of children were desensitized in the OIT group. In the OIT group, 28% passed the OFC at 24 months and were considered to achieve SU. HE OIT induces desensitization and tolerance in 35%-94% and 28%-78% of patients with HE allergies, respectively.\(^{30,34-36}\) Similarly, CM OIT results in desensitization and tolerance in 37%-100% and 23%-45% of patients allergic to CM, respectively.\(^{22,37,38}\)

Adverse reactions

Although OIT is known to induce desensitization or SU in FA patients, 30%-80% of patients experience adverse reactions such as mucocutaneous symptoms, bronchospasm, abdominal pain, vomiting, and anaphylaxis during the build-up phase (Table 1).\(^{25,36,39,40}\) The adverse rates
per dose were 6.5%-31%, and the adverse rates per patient were 30%-100%.\textsuperscript{34,39-41} Symptoms usually manifest during the build-up phase, but they may also arise during maintenance phase in certain instances. Additionally, adverse reactions related to OIT can be triggered by various factors, including exercise, bathing, acute infections, and psychological stress. Eosinophilic esophagitis (EoE) has been reported in 1-2.7% of patients who undergo OIT for allergies to HE, CM, or peanuts.\textsuperscript{42,43} Symptoms are often nonspecific and may include abdominal discomfort, pain, regurgitation, and vomiting.\textsuperscript{42} Therefore, suspicion and careful evaluation by a gastroenterologist, including an esophagastroduodenoscopy and biopsy, are necessary to ensure a proper diagnosis and appropriate therapeutic plan. It remains unclear which patients are at an increased risk of developing EoE during OIT, and further research is needed to identify risk factors and assess the prognosis of EoE.

Some patients can experience psychological stress and anxiety due to repeated adverse reactions, influencing the patient’s motivation and clinical outcomes of OIT.\textsuperscript{30,32} A recent study showed that more than 80% of patients sought psychological support for emotional problems and eating difficulties during the initial and build-up phases of OIT.\textsuperscript{44} Therefore, clinicians should be aware of patients’ emotional problems and provide psychological support when patients are required to cope with difficulties related to OIT to improve adherence to the treatment. The anxiety levels of patients and caregivers may temporarily increase, but previous studies have shown that OIT eventually improves the caregiver's QoL compared to before the OIT.\textsuperscript{45,46} The QoL of caregivers improved significantly when the maintenance phase was reached and 6 months after the maintenance phase started.\textsuperscript{46} Therefore, OIT can help reduce the psychological burden as long as there are no serious psychological problems severe enough to make it difficult to proceed with the long-term OIT process.\textsuperscript{45}

The action plan for patients and caregivers includes possible side effects, management of adverse reactions, observation time after treatments, and subsequent OIT schedules.
Additionally, bidirectional communication is needed so that patients or caregivers can participate in the decision-making process and consult with an allergist if they have any questions or suggestions during OIT.\textsuperscript{18,23} Most of the adverse reactions were mild and self-limited, and there were no reports of OIT-related deaths; however, up to 20% of patients discontinued OIT due to frequent allergic reactions and serious anxiety.\textsuperscript{30,41}

**Home-based up-dosing and modified immunotherapy protocols**

Various OIT protocols have been reported to ensure safe up-dosing at home to overcome the inconvenience of conventional OITs that have frequent adverse reactions and require hospital visits during the build-up phase (Table 2). Slow OIT protocols with a maintenance dose much less than the full dose have been developed for children with severe FAs for the purpose of safe OIT and avoidance of accidents due to hidden allergen exposure.\textsuperscript{47} In our previous study, children in the OIT group increased the amount of boiled EWs by 5% per day at home and a 25% increase per month at hospitals with a target dose of 4.0 g of boiled EW proteins (Figure 1).\textsuperscript{48} After completing a 5- to 13-month build-up phase, 93.8% (15/16) of patients with OIT showed desensitization, while only 6.2% (1/16) of patients in the control group passed OFC tests. Adverse reactions occurred in 75.0% of patients with OIT including 25% of anaphylaxis cases. Notably, no patients demonstrated serious anxiety or life-threatening events, which are the biggest obstacles to maintaining OIT. A Spanish clinical trial also performed a home-based OIT using pasteurized EWs and showed an 84.2% desensitization rate and a 90.8% adverse reaction rate in patients with OIT.\textsuperscript{36}

CM OIT is also associated with frequent adverse reactions, leading to treatment discontinuation.\textsuperscript{49,50} Therefore, modifications to the OIT protocol, such as adjustments to the speed and degree of up-dosing and processing of the consumed food itself, have been explored.
OIT protocols using heated or baked milk have been developed for safe up-dosing, as the heating or baking process reduces allergenicity by destroying conformational epitopes.\textsuperscript{51) Recent studies have shown that 60\%-80\% of children with IgE-mediated CM or HE allergies tolerate baked milk or eggs.\textsuperscript{18,52} However, the baked milk OIT protocol showed a low desensitization rate of less than 70\% for unheated milk (UM), which did not eliminate concerns about CM exposure in real life despite less frequent adverse reactions of 8\%-33\%.\textsuperscript{53-55}) To address these issues, Takahashi et al. used CM heated in a microwave oven for OIT.\textsuperscript{22}) When the volume of heated milk (HM) reached 200 mL, patients consumed 200 mL of HM every day for 2 months at home, then shortened the time to heat the CM in the microwave, and then switched to 200 mL of UM. After a 2-week off-treatment, 22.6\% of the subjects passed the OFC test. Another Japanese study conducted OIT with a small amount of CM (3 mL) after randomization into HM and UM in patients with CM allergy over 5 years of age.\textsuperscript{21}) After 1 year, 18\% of patients in the HM group and 31\% in the UM group passed the 25 mL OFCs, showing no statistically significant difference.\textsuperscript{21}) On the other hand, it was found that moderate-to-severe adverse responses were significantly lower in the HM group (0.7\%) than in the UM group (1.2\%) during OIT, which can induce immunological changes more safely when HM is used on the OIT compared UM.\textsuperscript{21, 47}) 11,56\textsuperscript{57,58}}

\textbf{The use of adjunctive therapies during OIT}

Adjunctive therapies with biologics, ketotifen and leukotriene receptor antagonists (LTRAs) have been developed to improve the efficacy and safety of OIT by blocking allergic reaction downstream effects by targeting IgE or mast cell mediators.\textsuperscript{59,29,60} Above all, Omalizumab has been used as an adjuvant during the dose escalation period to reduce adverse reactions and
improve efficacy. For example, Wood et al. showed that the omalizumab group took less time to reach the maintenance phase, although the desensitization rate and sustained unresponsiveness did not differ significantly from those of the CM OIT alone group. A recent real-world study conducted in Spain investigated 58 children with severe CM allergy treated with omalizumab. In that study, 83% of patients tolerated ≥ 6,000 mg of CM protein during the maintenance phase, and 40.5% of patients who completed follow-up tolerated CM without omalizumab. Notably, anaphylaxis occurred in 36.4% of patients who discontinued omalizumab, with a higher incidence in those who discontinued suddenly (50.0%) than gradually (12.5%). Recently, it has been suggested that calculating the dosage of omalizumab per body weight yields better clinical outcomes during the initial escalation phase than using the standard dosage per weight and total IgE levels. Additionally, ketotifen and LTRAs were reported to prevent adverse reactions, especially gastrointestinal symptoms, during OIT with HE, CM, wheat, or peanuts in previous studies. Studies using other biologics have also been conducted, such as the use of dupilumab (NCT03793608) or anti-IL-33 (NCT0290021) during peanut OIT, raising expectations for their use in HE or CM immunotherapy.

**Recommendations and contraindications of OIT**

OIT is a treatment whereby the food allergen, which had been strictly restricted for fear of serious allergic reaction in the past, is ingested regularly; therefore, OIT requires careful supervision according to the predetermined schedule due to the possibility of adverse reactions. Patients and their caregivers should be prepared to recognize and deal with allergic reactions during OIT. However, previous history of anaphylaxis to the targeted food or multiple FA is not a contraindication to OIT. Patients should not take allergens on an empty stomach or go to bed within 1 to 2 hours after administration. Additionally, hot showers or
baths, physical exertion, infection, gastrointestinal disease, dental procedures or surgeries, menstruation, lack of sleep, and uncontrolled underlying allergic diseases may increase the likelihood of adverse reactions during OIT.\textsuperscript{14,32}

There is still no consensus on the best age for OIT, but it is challenging to start in infancy due to limitations in the expression of symptoms that may occur during the treatment period.\textsuperscript{17} Although guidelines suggest that OIT can be considered from around 4 to 5 years of age, the starting age of OIT may depend on the patient's developmental status, the family's situation, the severity of the allergic reaction, and the risk-benefit ratio.\textsuperscript{14,16} For the safe provision of OIT, weak willingness, poor adherence to instruction, reluctance to use medications, severe anxiety, language barriers, and psychiatric problems should be evaluated before the treatment.\textsuperscript{17,44} It is noted that OIT is absolutely contraindicated if the patient has uncontrolled asthma, malignancy, active systemic autoimmune disorders, or diseases requiring treatment with beta-blockers.\textsuperscript{14,23} Relative contraindications include active severe atopic dermatitis, EoE, eosinophilic gastrointestinal diseases, mastocytosis, and heart diseases.\textsuperscript{17} During OIT, gastrointestinal symptoms should be monitored, as an increase of IgG4 and activated allergen-specific Th2 cells may affect the development of EoE.\textsuperscript{67}

**Future directions in studies for food oral immunotherapy**

According to the results of studies in patients with IgE-mediated peanut allergy, elevated concentrations of IgG4 and low levels of IgE to Ara h 2 were found in patients who acquired immune tolerance, whereas high levels of Ara h 2-specific IgE and Th2A cells were associated with persistent allergies.\textsuperscript{66,68} A recent study demonstrated that the possibility of tolerance is likely to be higher in young children with a low specific IgE, high threshold, and no experience of anaphylaxis, even with shorter OIT periods at small doses, suggesting that the immune and
clinical phenotypes of FA may be related to the outcomes of immunotherapy.\textsuperscript{69) However, few studies have examined which subgroup responds well to OIT, although biomarker identification and subgroup analysis may provide better individualized treatment options in FA. Moreover, the OIT protocol needs to be standardized, and there needs to be more research investigating the mechanisms and long-term effectiveness of food immunotherapy. Given these gaps, questions remain regarding the time needed to reach tolerance and appropriate biomarkers of OIT. Not surprisingly, treatment of multiple FAs is of growing interest because approximately 30% of children with FAs suffer from allergies to more than one food, and single-food OIT does not significantly improve QoL.\textsuperscript{70,71) Further clinical trials are needed to assess the safety and efficacy of multi-OIT protocols for patients with multiple FAs.

Conclusion

Children with HE or CM allergies are at risk of nutritional deficiencies and psychological problems. OIT could be a safe and effective option to induce desensitization in FA patients. However, the risk of adverse events during OIT remains a concern. Thus a personalized action plan should be provided to patients and their caregivers to treat possible allergic reactions. The patient's inability to cope with protocol, uncontrolled asthma, and psychiatric barriers should be assessed before initiating the OIT. Recent studies suggest that many promising adjunctive therapies might help patients optimize the administration of OIT. However, discontinuation of omalizumab can be associated with severe allergic reactions during OIT and should be carefully monitored. Unfortunately, there is a paucity of literature regarding clear indications of OIT and standard protocols according to clinical and immunological characteristics. Further studies should not only determine which specific phenotyping of FA patients would benefit the
most from OIT, but also which therapeutic options or dosing schedules could be applied to
approach immune tolerance.
**Figure Legend**

Figure 1. Two protocols of oral immunotherapy: conventional oral immunotherapy (A) and modified oral immunotherapy (B).
References


Gruzelle V, Juchet A, Martin-Blondel A, Michelet M, Chabbert-Broue A, Didier A.


<table>
<thead>
<tr>
<th>Type of adverse reactions</th>
<th>Symptoms</th>
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<tbody>
<tr>
<td>Skin/mucosal</td>
<td>Pruritus, urticaria, or angioedema</td>
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<tr>
<td>Conjunctival</td>
<td>Eye itching, injection, or tearing</td>
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</tbody>
</table>
| Respiratory tract                  | Upper: rhinorrhea, nasal congestion, tightness in the pharyngolarynx, barking cough, stridor, hoarseness  
|                                   | Lower: coughing, wheezing, dyspnea, chest tightness, or need for supplemental oxygen/mechanical support |
| Gastrointestinal                   | Nausea, abdominal pain or discomfort, vomiting, or diarrhea             |
| Cardiovascular or neurologic       | Reduced BP, hypotonia, or syncope                                        |
| Psychological                      | Stress, anxiety, emotional problems, eating difficulties                 |
Table 2. Summary of recently published studies regarding modified oral immunotherapy protocols for egg or milk allergy

<table>
<thead>
<tr>
<th>Country</th>
<th>Study design</th>
<th>Number of participants (Treatment/Control)</th>
<th>Median Age (yr, range)</th>
<th>Foods</th>
<th>Increment interval during the build-up phase</th>
<th>No. of patients with AE during the build-up phase</th>
<th>Duration of dosing up (range)</th>
<th>Desensitization rate</th>
<th>Maintenance dose (= target dose)</th>
<th>Duration of maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>United Kingdom(^{(2)})</td>
<td>Case series</td>
<td>15 (15/0)</td>
<td>11.2 (6-17)</td>
<td>Baked egg biscuits</td>
<td>daily</td>
<td>73% (11/15), mild reactions</td>
<td>60-270 days</td>
<td>53% (8/15)</td>
<td>16 biscuits squares (equivalent to 6.25 g of egg protein)</td>
<td>N/A</td>
</tr>
<tr>
<td>Spain(^{(3)})</td>
<td>RCT</td>
<td>101(76/25)</td>
<td>6.9 (6-9)</td>
<td>Pasteurized EW</td>
<td>Pattern I, 5% per day at home and 30% per week at the hospital; Pattern II 30% per week at the hospital</td>
<td>Pattern I, 23/25 (92%); Pattern II: 43/47 (91.48%)</td>
<td>96.00 (7-329) days</td>
<td>64/76 (84.2%)</td>
<td>30 mL of pasteurized EW</td>
<td>12 mo</td>
</tr>
<tr>
<td>Japan(^{(4)})</td>
<td>Non-randomized study</td>
<td>133 (104/29)</td>
<td>6 (5-7)</td>
<td>Boiled EW</td>
<td>10%-30% per mo</td>
<td>56.0% (47/84)</td>
<td>12 mo</td>
<td></td>
<td>OIT group: 34.7% (34/98) Control group: 11.1% (3/27)</td>
<td>N/A</td>
</tr>
<tr>
<td>Korea(^{(5)})</td>
<td>Case-control study</td>
<td>32 (16/16)</td>
<td>5% per day at home and 25% per month at hospital</td>
<td>OIT group: CoFAR grade 1 – 75% (12/16) CoFAR grade 2 - 13% (2/16) Untreated group: 75% (12/16)</td>
<td>Boiled EW</td>
<td>7 (5-13) mo</td>
<td>OIT group: 94% (15/16) Control group: 6% (1/16)</td>
<td>40 g of boiled EW</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Country</td>
<td>Study Type</td>
<td>Number of Participants</td>
<td>Treatment</td>
<td>Dose</td>
<td>% Response</td>
<td>Duration</td>
<td>Initial Dose</td>
<td>Advantages</td>
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<tr>
<td>Japan</td>
<td>Non-randomized study</td>
<td>48 (31/17)</td>
<td>HM</td>
<td>1.2-fold every 2 hr</td>
<td>64% (21/31)</td>
<td>1 yr: 45% (14/31) 2 yr: 60% (18/30) 3 yr: 70% (21/30) 4 yr: 85% (17/20)</td>
<td>Control group: 0.0% (0/17)</td>
<td>200 mL of HM</td>
<td>1-4 yr</td>
<td></td>
</tr>
<tr>
<td>Japan</td>
<td>Non-randomized study</td>
<td>50 (41/9)</td>
<td>Whole milk</td>
<td>10-50% per mo</td>
<td>37.8% (14/37)</td>
<td>OIT group: 37.5% (15/40) Control group: 0.0 % (0/9)</td>
<td>10 times greater than the initial dose</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Japan</td>
<td>RCT</td>
<td>17 (HM) and 16 (UM)</td>
<td>HM: 7.6 (5.5-11.2) vs. UM: 6.1 (5.3-10.8)</td>
<td>HM or UM every 5 days</td>
<td>HM 4.3 vs. UM 6.1</td>
<td>UM 75% and HM 94% ($P=0.17$)</td>
<td>3 mL of HM or UM</td>
<td>1 yr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>USA</td>
<td>RCT</td>
<td>30 (15/15)</td>
<td>Baked milk (muffin)</td>
<td>33-100% every 10-21 days</td>
<td>100% vs. 73%</td>
<td>11/15 (73%) vs. 0/15 (0%)</td>
<td>2 g of baked milk protein</td>
<td>1 yr (total treatment)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AE, adverse effects; OIT, oral immunotherapy; EW, egg white; RCT, randomized controlled trial; UM, unheated milk; HM, unheated milk; CoFAR, Consortium of Food Allergy Research.
### Table 3. Contraindications of oral immunotherapy for food allergies

<table>
<thead>
<tr>
<th>Contraindications</th>
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<tbody>
<tr>
<td>Poor adherence to instruction</td>
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<tr>
<td>Reluctance to use medication</td>
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<tr>
<td>Severe anxiety</td>
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<tr>
<td>Uncontrolled asthma or severe atopic dermatitis</td>
</tr>
<tr>
<td>Malignancy</td>
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<tr>
<td>Active systemic autoimmune disorders</td>
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<tr>
<td>Diseases requiring beta-blockers</td>
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<tr>
<td>Eosinophilic esophagitis</td>
</tr>
<tr>
<td>Eosinophilic gastrointestinal diseases</td>
</tr>
<tr>
<td>Mastocytosis</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
</tr>
</tbody>
</table>
Figure 1

(A) Initial escalation - (25% increments per 2 weeks at hospital)

(B) Initial escalation - (5% daily increments at home and 25% increments per month at hospital)