International Archives of Allergy and Immunology

Clinical Allergy – Research Article

Int Arch Allergy Immunol 2020;181:699–705
DOI: 10.1159/000508627

Received: February 21, 2020
Accepted: May 13, 2020
Published online: June 22, 2020

Single-Center Noninferiority Randomized Trial on the Efficacy and Safety of Low- and High-Dose Rush Oral Milk Immunotherapy for Severe Milk Allergy

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Keywords
Oral immunotherapy · Milk allergy · Safety · Efficacy · Oral food challenge test

Abstract
Introduction: Oral immunotherapy (OIT) has been reported to be effective but associated with a risk of severe symptoms. Thus, an OIT method with decreased risk is required. ***Objectives:*** We aimed to evaluate the efficacy and safety of low- and high-dose OIT regimens in children with severe milk allergy. ***Methods:*** Overall, 33 participants (median age, 9 years; median final dose of the milk oral food challenge [OFC], 2 mL) were included. The participants were randomly assigned to groups that received either a low (20 mL; $n = 19$) or high (100 mL; $n = 14$) maintenance target dose of OIT. The dose was gradually increased to the target dose in the rush escalation phase and was then maintained daily at home. The primary endpoint was the final OFC dose at 6 months of OIT. Adverse events during OIT were evaluated. ***Results:*** The final OFC dose after OIT was significantly higher than that before OIT in both groups (low-dose, $p = 0.000$; high-dose, $p = 0.006$), but there was no significant difference in the final OFC dose between the 2 groups ($p = 0.767$). In the maintenance phase, the high-dose group had significantly more severe symptoms than did the low-dose group (0.5%, 11/2,355 total intake events vs. 0.1%, 4/3,230 total intake events; $p = 0.018$). ***Conclusions:*** An equally increased dose effect was observed for maintenance OIT doses of 20 and 100 mL in children with severe milk allergy. The risk of severe symptoms in the maintenance phase was lower in the low-dose group. A low-dose OIT regimen is recommended for severe milk allergy.

Edited by: H.-U. Simon, Bern.

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Introduction

Milk allergy is one of the most common food allergies in children worldwide [1]. Allergen-specific immunotherapy (AIT) for immunoglobulin E (IgE)-mediated milk allergies has been used in the management of allergic disorders [2–4]. AIT for milk allergy is mainly through oral immunotherapy (OIT), but sublingual immunotherapy and epicutaneous immunotherapy have also been reported [3]. OIT is administered in 2 phases: the escalation phase in which the allergen dose is increased and the maintenance phase in which the dose is maintained. Rush OIT is a method for performing a time-consuming escalation phase in a short time. Rush OIT is expected to induce desensitization in children with IgE-mediated milk allergy [2]. However, a major limitation of AIT is the occasional induction of severe adverse events [2, 3]. Yanagida et al. [5] reported that low-dose milk OIT is safer for severe milk allergy. However, no randomized trial has compared the efficacy and safety between low- and high-dose rush OIT. Thus, this study aimed to evaluate the efficacy and safety of low- and high-dose oral immunotherapy regimens in children with severe milk allergy to ultimately identify an effective and safe maintenance dose of rush OIT for severe milk allergy. Toward this goal, we conducted rush OIT using 2 target doses: low (20 mL) and high (100 mL).

Materials and Methods

Participants and Sample Size Estimation

This was a randomized trial of children who had tested positive for the fresh milk oral food challenge (OFC) at Osaka Habikino Medical Center between 2013 and 2018. The inclusion criteria were age 5–15 years, positive result with a final dose of ≤10 mL in the milk OFC, and written informed consent from the parents or legal guardians. The severity of the OFC result was assessed by the attending physician in accordance with the modified Sampson's anaphylaxis grades in the Japanese Pediatric Guideline for Food Allergy (JPGFA) 2014 [2]. Blood samples were also collected to assess allergen-specific IgEs.

We calculated the power for a noninferiority test assuming there was no difference among samples of size 30, and thus, the optimal sample size was determined to be 30 participants due to feasibility, 15 each for the low- and high-dose group. It was determined that 20 mL would yield the same effect as 100 mL if the proportion of those with an OFC threshold of ≥50 mL after 6 months in the low-dose group was the same or was not <10% (the difference of efficient participants between groups was less than 2) in the high-dose group. Under the condition, the probability of the difference of efficient participants between groups of 1 or less is 71.4% when there is really no difference between groups. In addition, when a true difference between groups exists, the probability that a difference between groups is determined is 50.2, 71.4, and 87.4% when the true difference is 10, 20, and 30%, respectively. Therefore, if it was inferior by >20%, there was a sufficient probability of there being a difference between groups.

OIT Protocol

The participants were randomly assigned into the target dose groups of 20 or 100 mL in a 1:1 ratio. Using a piece of software developed by one of the authors, Ito, the participants were allocated at the data management center of Osaka Habikino Medical Center. Allocation was based on minimalization stratified by age, milk-specific IgE, and the final dose of milk OFC before OIT.

The patients ingested an initial dose of milk at about one-tenth of the threshold, which was increased to the target dose by about 20% at each of the 4 doses per day at the hospital. The method of increase during the escalation phase was the same in both groups up to the 20 mL dose. Then, for the high-dose group, 9 more steps were added (25, 30, 35, 42, 50, 60, 72, 84, and 100 mL). Symptoms were treated with drugs as needed. If symptoms were observed frequently or at less than the threshold level before OIT, administration of antihistamines and leukotriene receptor antagonists was initiated and continued during the maintenance phase.

If symptoms occurred 3 times at the same dose before reaching the target dose, we stopped increasing the dose and determined the maintenance dose as the maximum dose without symptoms. The participants were instructed to ingest the target dose every day at home. The participants and their guardians were instructed to record the intake status and induced symptoms at home in the participants' diaries. They were evaluated through inquiries based on intake diaries by parents during monthly outpatient visits.

After 6 months of the maintenance phase, OFCs were repeated and blood samples collected. The patients were instructed to avoid milk intake on the day before an OFC. Antihistamine and leukotriene receptor antagonist therapies were stopped for 3 days and 1 day, respectively, before an OFC, in accordance with the method described in the JPGFA 2014. For the first OFC, doses (in the sequence 1, 2, 5, 10, and 20 mL) of fresh milk were consumed every 20 min according to the method described. The patients with negative results underwent further fresh milk OFCs with 50 and 100 mL.

Outcome Measures

The primary endpoint was the threshold determined in the milk OFC after 6 months of the maintenance phase. If the difference in the number of participants whose OFC threshold was 50 mL or more remained within 10% (2 participants) in both groups, this was determined as no significant difference.

The secondary endpoint was safety. The number of symptoms and the number of epinephrine doses used in the escalation and maintenance phases and the number of emergency visits in the maintenance phase were compared between the 2 groups. In the maintenance phase, safety was assessed using the participant's diary and medical interviews during the outpatient visits. We evaluated the strength of induced symptoms at home according to classification of anaphylaxis grading scales and treatment [6]. The results of blood tests and skin prick tests before the start of OIT and during the maintenance phase (at 6 months) were also evaluated as secondary endpoints in both groups. We measured milk-, casein-, and β-lactoglobulin-specific IgE titers (Thermo Fisher Sci-

entific-Phadia, Uppsala, Sweden) before treatment and at 6 months of the maintenance phase. A prick test was performed before OIT and after 6 months of the maintenance phase using a bifurcated needle® (Tokyo M I Commerce, Tokyo, Japan) with positive (histamine dihydrochloride, 10 mg/mL) and negative (saline) controls and the milk prick solution® (Torii Pharmaceutical Co., Tokyo, Japan). A positive skin prick test was defined as a wheal diameter of ≥3 mm larger than that in the negative controls. The diameter of the flare area was not considered in the outcome of the skin prick test. All procedures were performed in accordance with the JPGFA 2014 guidelines [2].

Evaluation of Treatment Compliance

Treatment compliance rate was evaluated by comparing the ratio of participants who reached the target maintenance dose (100 or 20 mL) at the end of the escalation phase between the 2 groups. Per-protocol analysis of outcome was performed on them. The evaluation of compliance rate during the 6-month maintenance phase was also conducted using the food diary and examination between the 2 groups.

Statistical Analysis

We performed intent-to-treat (ITT) analysis, and per-protocol analysis was added as needed. The Mann-Whitney *U* test and Wilcoxon signed-rank test were used for between-group comparisons of continuous variables such as age, number of food allergens, final dose in the OFC, antigen-specific IgE titers, and wheal diameter in the milk prick test of independent samples and corresponding samples, respectively. Meanwhile, categorical variables such as sex, other allergic diseases, symptom details, and medication were compared between the 2 groups using Fisher's exact test and χ^2 tests. All statistical analyses were performed using IBM SPSS Statistics version 22 (New York, USA), and a 2-tailed p value of <0.05 was considered statistically significant.

Results

Patient Characteristics

Of the 38 children with severe milk allergy examined, 33 children with positive OFC results at <10 mL of the final dose provided written informed consent and were enrolled. The median age was 9 years (range, 5–15 years), and the median final dose in the milk OFC was 2 mL. In total, 19 and 14 participants were randomly assigned to the low-dose and high-dose groups in a 1:1 ratio (online suppl. Fig. 1; for all online suppl. material, see www.karger.com/doi/10.1159/000508627). There were no significant differences in the clinical characteristics, final dose of the OFC before OIT, and antigen-specific IgEs between the 2 groups (online suppl. Table 1). Overall, 17 (90%, 17/19) and 9 (64%, 9/14) participants in the low- and high-dose groups, respectively, reached the target maintenance dose during the escalation phase ($p = 0.106$). One participant in the low-dose group discontinued the OIT because of symptom intolerance.

The dose was reduced during the maintenance phase because of symptoms in 6 participants in each group. One participant in the high-dose group discontinued OIT because of severe symptoms. The median maintenance doses at the end of OIT were 45 and 20 mL, respectively, in the high-dose and low-dose groups, and the dose was significantly higher in the high-dose group ($p = 0.001$). At the end of OIT, 58% (19/33) of patients were under treatment with antihistamines and 51% (17/33) of patients were under treatment with leukotriene receptor antagonists to prevent adverse reactions or treat other allergic diseases such as allergic rhinitis.

OFC Results after 6 months

OFC was performed after 6 months of the maintenance phase in 18 participants in the low-dose group and 13 participants in the high-dose group who had undergone OIT. The details of OFC results before and after OIT in both groups are given in online suppl. Tables 2 and 3. The final OFC dose after OIT significantly improved before and after OIT in both groups (low-dose, $p = 0.000$; high-dose, $p = 0.006$). The final positive dose of OFC after OIT was lower than the maintenance dose at the end of OIT in 9 of 14 (64%) patients in the high-dose group and 5 of 19 (26%) patients in the low-dose group. The median final OFC dose after OIT was 10 mL (range, 2–100 mL) in the low-dose group and 20 mL (range, 2–100 mL) in the high-dose group. In total, 3 and 4 participants in the low- and high-dose groups, respectively, had a final OFC dose of ≥50 mL (Fig. 1). The final OFC dose after OIT was not significantly different between the 2 groups ($p = 0.767$).

The per-protocol analysis included 17 subjects in the low-dose group and 9 subjects in the high-dose group who reached the target maintenance dose in the escalation phase. The median OFC dose after 6 months was 10 mL in the low-dose group and 20 mL in the high-dose group, with no significant difference ($p = 0.367$). There were 3 subjects in both groups whose threshold in the OFC was ≥50 mL (Fig. 1). These indexes significantly improved before and after OIT in both groups ($p = 0.000$ for both groups).

Milk-, Casein-, and β-Lactoglobulin-Specific IgE Antibody Titer and Milk Prick Test after 6 Months of Maintenance Phase

The milk-, casein-, and β-lactoglobulin-specific IgE titers and wheal diameter from the milk prick tests after 6 months of the maintenance phase were not significantly different between the 2 groups ($p = 0.763$, 0.980, 0.268,

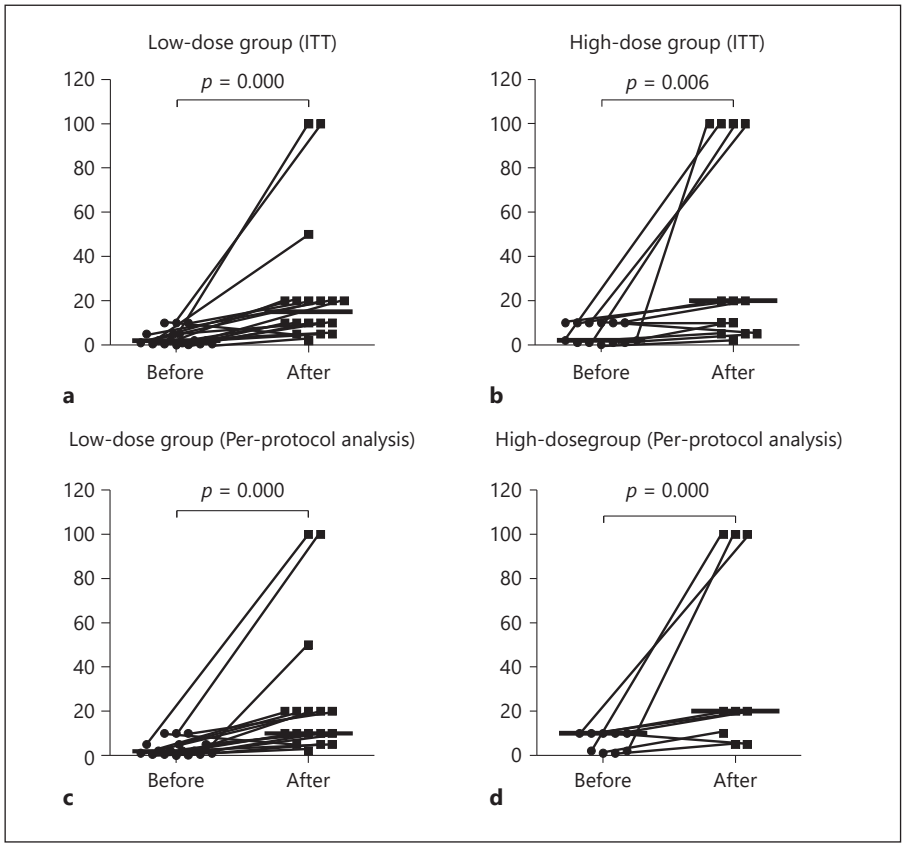

Fig. 1. ITT analysis of the final dose of milk (high-dose group (**a**); 20-mL group (**b**)) in the oral food challenge before and after OIT. Per-protocol analysis of the final dose of milk (100-mL group (**c**); 20-mL group (**d**)). The graph shows raw data points and median. The details of OFC, including the final dose in the 100- and 20-mL groups, are described in online suppl. Tables 2 and 3. Significance was set at $p < 0.05$ using the Wilcoxon signed-rank test. OIT, oral immunotherapy; OFC, oral food challenge; ITT, intent-to-treat.

and 0.185, respectively; online suppl. Table 4). However, compared with the levels before OIT, casein- and β-lactoglobulin-specific IgE levels were significantly lower at 6 months after OIT in both groups. Furthermore, the milk-specific IgE value in the high-dose group and the wheal diameter in the milk prick test in the low-dose group were significantly reduced at 6 months after OIT.

Adverse Events

Escalation Phase

The ITT analysis showed no significant differences in the number of adverse events and severe symptoms in the escalation phase between the 2 groups (Table 1). Adverse events occurred in 92 (22%) and 117 (26%) of a total of 412 and 447 intake events in the low- and high-dose groups, respectively ($p = 0.204$; Table 1). Epinephrine was used for severe symptoms in 6 of 8 (8 of a total 412 of intake events, 1.9%) patients who developed severe symptoms in the low-dose group and in 5 of 9 (9 of a total of 448 intake events, 2.0%) patients who developed severe symptoms in the high-dose group (Table 1). There was no significant difference in the use of epinephrine during the escalation phase ($p = 0.766$). The intake doses when epinephrine was used were 0.35, 3, 6, 8.5, 10, and 20 mL for the low-dose group and 0.6, 7.2, 30, and 60 mL for the high-dose group.

In the per-protocol analysis, the total numbers of adverse events and mild symptoms were significantly higher in the high-dose group ($p = 0.034$ and $p = 0.020$, respectively), but there was no significant difference in moderate and severe symptoms between the 2 groups ($p = 0.197$ and $p = 0.747$, respectively).

Maintenance Phase

The rate of adverse events was not significantly different between the low- and high-dose groups (8.9 vs. 5.3%, $p = 0.096$; Table 2). However, the low-dose group had significantly more mild symptoms than the high-dose group (6.3% [231/3,230] vs. 2.7% [64/2,355]; $p = 0.000$), whereas the high-dose group had significantly more severe symptoms than the low-dose group (0.1% [4/3,230] vs. 0.5% [11/2,355]; $p = 0.018$). The frequency of epinephrine use was also significantly higher in the high-dose group than in the low-dose group (0.3% [6/2,355] vs. 0.03% [1/3,230]; $p = 0.047$).

Table 1. Adverse events at the escalation phase during OIT[a]

	Low-dose (20 mL) group (n = 19)	High-dose (100 mL) group (n = 14)	p value[b]
Intake events, n	412	448	
Allergic symptoms, n (%)	92/412 (22)	117/448 (26)	0.204
Mild	26/412 (6.3)	38/448 (8.4)	0.244
Moderate	58/412 (14)	70/448 (16)	0.565
Severe	8/412 (1.9)	9/448 (2.0)	1.000
Symptom details (including overlapping) (%)			
Skin	57/412 (14)	93/448 (21)	0.009
Gastrointestinal tract	35/412 (8.5)	27/448 (6.0)	0.187
Respiratory tract	40/412 (9.7)	29/448 (6.5)	0.102
Cardiovascular	3/412 (0.7)	6/448 (1.3)	0.509
Neurological	3/412 (0.7)	3/448 (0.7)	1.000
Medication, n (%)			
Oral antihistamine	45/412 (11)	79/448 (18)	0.006
Bronchodilator	31/412 (7.5)	26/448 (5.8)	0.339
Epinephrine	6/412 (1.5)	5/448 (1.1)	0.766

OIT, oral immunotherapy. [a] The strength of induced symptoms at the escalation phase was evaluated based on the classification of severities according to clinical symptoms [5]. [b] Statistically significant differences were assessed using Fisher's exact test. $p < 0.05$ was considered statistically significant.

Table 2. Adverse events during the maintenance phase of OIT[a]

	Low-dose (20 mL) group (n = 19)	High-dose (100 mL) group (n = 14)	p value[b]
Intake events, n	3,230	2,355	
Allergic symptoms, n (%)	286/3,230 (8.9)	125/2,355 (5.3)	0.096
Mild	231/3,230 (6.3)	64/2,355 (2.7)	0.000
Moderate	51/3,230 (1.6)	50/2,355 (2.1)	0.154
Severe	4/3,230 (0.1)	11/2,355 (0.5)	0.018
Symptom details (including overlapping) (%)			
Skin	138/3,230 (4.3)	100/2,355 (4.3)	1.000
Gastrointestinal tract	72/3,230 (2.2)	31/2,355 (1.3)	0.012
Respiratory tract	104/3,230 (3.2)	73/2,355 (3.1)	0.817
Cardiovascular	0/3,230 (0)	2/2,355 (0.1)	0.178
Medications, n (%)			
Oral antihistamine	144/3,230 (4.5)	113/2,355 (4.8)	0.561
Bronchodilator	79/3,230 (2.5)	55/2,355 (2.3)	0.860
Epinephrine	1/3,230 (0.03)	6/2,355 (0.3)	0.047

OIT, oral immunotherapy. [a] The severity of induced symptoms at the escalation phase was evaluated based on the classification of severities according to clinical symptoms [5]. [b] Statistically significant differences were assessed using Fisher's exact test. $p < 0.05$ was considered statistically significant.

In the per-protocol analysis, the total number of adverse events was not significantly different between the 2 groups (p = 0.168). The low-dose group had significantly milder (p = 0.000) symptoms, while the high-dose group had significantly more moderate symptoms (p = 0.03). The number of severe symptoms was not significantly different (p = 0.142). Epinephrine was used twice in the high-dose group, but it was not used in the low-dose group.

Discussion/Conclusion

In the current study, we evaluated the efficacy and safety of low- and high-dose OIT for severe milk allergy in a randomized trial. We found that the effect of the low dose was similar to that of the high dose. Furthermore, the symptoms in the low-dose group tended to be milder during the maintenance phase than those in the high-dose group.

In both groups, the final dose of OFC was significantly increased before and after OIT, and casein- and β-lactoglobulin-specific IgE levels were significantly lower at 6 months after OIT. The effect of OIT was observed in both groups. The effect of rush OIT in severe milk allergy has been reported by Takahashi et al. [7], who performed OIT using microwave-heated cow's milk in 31 children. Of these, 8 children achieved 2 weeks of sustained unresponsiveness to cow's milk at 1 year from the start of OIT. No children in the control group passed.

However, the final positive dose of OFC after OIT was lower than the maintenance dose at 6 months in 9 out of 14 (64%) patients in the high-dose group and 5 out of 19 (26%) patients in the low-dose group (online suppl. Tables 2, 3). The explanation for this is probably that their desensitization was unstable because of the short OIT periods and small maintenance dose. Furthermore, the threshold doses in the final OFC may have been influenced by the short period of milk avoidance and the use of antihistamines and leukotriene receptor antagonists.

The final OFC dose after OIT was not significantly different between the 2 groups ($p = 0.767$), and the number of participants whose threshold was 50 mL or more in the final OFC after 6 months of maintenance phase did not significantly differ between the 2 groups. We considered that low dose and high dose did not differ in the effect of rush OIT for severe milk allergy. Kulis et al. [8] reported no significant differences in proallergic cytokines, including IL-5, IL-13, and IL-9, T cells, or basophils between low- and high-dose peanut OIT. Yanagida et al. [5] reported that the effect of increasing the threshold was observed by continuing a maximum of 3 mL of milk OIT in children severely allergic to milk. After 1-year OIT, OFC of 3 mL was negative in 58.3% (7/12) of the participants in the OIT group and 13.8% (4/25) of the participants in the placebo group ($p = 0.018$). Meanwhile, 33.3% (4/12) of the participants in the OIT group and 0.0% (0/25) of the participants in the placebo group were unresponsive to 25 mL of milk ($p = 0.007$).

In both the intention to treat and the per-protocol analyses, the symptoms during the maintenance phase were significantly less severe in the low-dose group than in the high-dose group. This indicates that the intensity of the induced symptoms could be reduced by reducing the maintenance dose. Yanagida et al. [5] reported that the most frequent symptoms of OIT up to 3 mL were mild, with 0% at the hospital and 0.03% at home. On the other hand, there was no significant difference between groups in the use of epinephrine during the escalation phase ($p = 0.766$). Since epinephrine use was required following a milk intake dose as low as 0.35 mL, it was considered that the risk of increasing the dose may be present even at low dose in OIT with severe milk allergy.

The limitations of this study include no blinding, no placebo comparator group, possibility of selection bias due to all participants being enrolled in the same hospital, and lack of generalizability of the findings to other populations. Sustained unresponsiveness has not been confirmed in this study, but such confirmation will be necessary for determining the effect of OIT in the future. We could not determine a minimum target maintenance dose to obtain the same effect as 20 mL. The effect of OIT of egg allergy is reported to be different depending on the allergen intake in mouse models [9]. At present, the maintenance dose of 20 mL is considered balanced in both efficacy and safety.

In conclusion, the effect of an increased dose was equally observed in both maintenance doses of 20 and 100 mL in rush OIT for children with severe milk allergy. The risk of adverse events, particularly severe symptoms, in the maintenance phase was lower in children who received maintenance doses of 20 mL. Low-dose rush OIT for severe milk allergy is effective, and thus it may be reasonable to consider increasing the dose slowly, prioritizing patient safety.

Acknowledgement

We extend our sincerest gratitude to the children who participated in the study and their guardians.

Statement of Ethics

This study was approved by the Ethics Committees of Osaka Habikino Medical Center (approval number 620, trial registration number: UMIN-CTR Clinical Trial-UMIN000012391 (https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000014490). Written informed consent was obtained from all parents or legal guardians of the participants.

Disclosure Statement

The authors have no conflicts of interest to declare.

Funding Sources

There were no funding sources.

Author Contributions

Yuri Takaoka, Yuko Yajima, Junko Kumon, Takahiro Muroya, Yuki Tsurinaga, Amane Shigekawa, Shinichi Takahashi, Norihito Iba, Taisuke Tsuji, Tomoki Nishikido, Yukinori Yoshida, Satoru Doi, and Makoto Kameda diagnosed and treated the children with allergies and recruited the participants. Yoichi M. Ito provided the allocation software and calculated the sample size. Yuri Takaoka, Yuko Yajima, and Makoto Kameda designed the research study. Yuri Takaoka and Makoto Kameda drafted the manuscript. All authors have read and approved the final manuscript.

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