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Efficacy and safety of low- and high-dose slow oral egg immunotherapy for hen's egg allergy: Single-center non-inferiority randomized trial

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Abstract

Background: Low-dose oral immunotherapy (OIT) is a safe treatment for hen's egg allergy; however, comparison of its therapeutic effects with those of high-dose OIT has not been reported.

Objective: To compare the efficacy of low- and high-dose boiled egg-white (EW) OIT for hen's egg allergy.

Methods: Patients with hen's egg allergy were randomly assigned to two groups: OIT using hard-boiled EW with a maximum maintenance dose of 2 and 20 g in the low-dose (L-D) and high-dose (H-D) groups, respectively. The intake dose was ingested twice a week, increased by approximately 20% per week until reaching the target maintenance dose (2 or 20 g hard-boiled EW), and maintained thereafter according to the schedule. The threshold was confirmed via oral food challenge (OFC) after 6 months, and the difference in the proportion of subjects passing the exit OFC between groups was evaluated.

Results: Fifty-two patients (L-D, n = 23; H-D, n = 29) were enrolled. Thirty-three patients (L-D, n = 17; H-D, n = 16) completed the 6-month OIT and underwent an exit OFC. In total, three (L-D, 3/17; H-D, 3/16) patients in each group tested negative for an exit OFC with a 20-g reactive dose (p = 1.000). EW-specific IgE levels in both groups decreased significantly after OIT (L-D, $p < 0.001$; H-D, $p = 0.002$).

Conclusion: A threshold-elevating effect was observed in the L-D group, not inferior to that in the H-D group. Low-dose OIT may be appropriate to treat hen's egg allergy for the first 6 months.

Key words: oral immunotherapy, egg allergy, safety, efficacy, low dose

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Introduction

Hen's egg allergy is one of the most common childhood food allergies in Japan. Yamamoto et al. reported that the prevalence of caregiver-reported immediate hen's egg allergy was 5.4% at 1 year of age in a cohort study.[1] Natural history of hen's egg allergy in Japanese children has been reported to be 30% in 3 years old and 66% in 6 years old.[2] Therefore, the development of an optimal treatment for hen's egg allergy is required. Immediate hen's egg allergies are mainly induced by a reaction to egg white, which include the main allergens ovalbumin (Gal d 2), which is easily coagulated by heating,

and ovomucoid (Gal d 1), which remains stable under thermal and chemical treatments.[3] On the other hand, allergens in the egg yolk include serum albumin (α-ribetine; Gal d 5), which is a causative allergen in the bird-egg syndrome.[4]

Allergen-specific immunotherapy, mainly oral immunotherapy (OIT), is used in the treatment of immunoglobulin E (IgE)-mediated hen's egg allergy; in addition, sublingual immunotherapy has been attempted.[5] OIT showed a dose-dependent effect on the treatment response. Burks et al. reported that among children with hen's egg allergies who received OIT using raw egg white powder at a dose that was increased to 2 g, 55% and 75% were desensitized after 10 and 22 months, respectively.[6] However, the risk of severe symptoms, which is higher during the dose-increasing phase than that during the maintenance phase, should be mitigated in OIT.[7]

Previously, in patients with egg allergy, we performed OIT using hypoallergenic cookies, which is a safer method, and a threshold-increasing effect was observed.[8] In both low- and high-dose OIT for milk allergy, although the dose-increasing effect was similar, the high-dose group showed more serious symptoms during the maintenance period than that shown by the low-dose group.[9] However, the efficacy of low-dose and high-dose egg allergy treatment has not been compared yet.

In this non-inferiority study, we examine whether the dose increasing effect of low-dose OIT is not inferior to that of high-dose OIT in children with moderate hen's egg allergy.

Methods

Participants

This randomized trial of open-labeled oral egg immunotherapy was conducted at Habikino Medical Center, Osaka, Japan from 2013 to 2018. We enrolled participants aged 3 to 15 years who showed a positive result in an open-labeled oral food challenge (OFC) test using hard-boiled egg white boiled at 100 degrees for 20 min. During the OFC, 1, 2, 5, 10, and 20 g of boiled egg white was consumed every 20 min. The severity of the symptoms observed during the oral boiled egg-white challenge test was determined based on Sampson's severity scores, as recommended in the Japanese Pediatric Guideline for Food Allergy (JPGFA), 2014.[10] Intensity of symptoms was expressed from a score of 1 to 5, representing mild to severe, for each organ, based on Sampson's severity scores. This study was approved by the Ethics Committee of Osaka Habikino Medical Center (approval number 730-1; trial registration number: UMIN-CTR Clinical Trial-UMIN000018142; https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000014490). Written informed consent was obtained from all the parents or legal guardians of the participants. For children over 7 years of age, the study was explained in plain language, and written informed consent was obtained from the parents or legal guardians of these children.

Sample Size Estimation

We determined that the enrollment of 24 patients in each group would provide a statistical power of 70% to determine non-inferiority, assuming that the negative rate of OIT was expected to be 80% in both groups, the one-sided alpha was 0.05, and the non-inferiority margin was 30%. To allow for attrition, we aimed to enroll 25 patients in each group. We assumed no significant difference was present in the OIT method based on our previous study.[11] OIT for wheat allergy was performed by dividing the frequency of allergen intake per week into two groups: low frequency (twice per week) and high frequency (more than 5 times per week). In the present study, 10 patients whose maintenance doses were lower than the target maintenance dose were subjected to OFC after the end of OIT, and 70% of had negative OFC results, being able to consume more than their maintenance dose. Therefore, even if the maintenance dose was low, we considered that the dose increasing effect could be observed. The negative rate of OIT was also expected to be 80%, based on a previous OIT study for wheat allergy.[11] We reported the proportion of cases with negative OFC or ingestion above the target dose after OIT was 75 % in the previous OIT study for wheat allergy.[11]

OIT protocol

Patients were randomly assigned at a ratio of 1:1 based on a maintenance target dose of 2 or 20 g to the L-D group or to the group with a high maintenance target dose for OIT (high-dose group; H-D group). Using software developed by one of the authors (Y.M.I.), the data management center of Osaka Habikino Medical Center performed allocation based on the minimization method,[8,9] which is based on the method of Pocock et al.[12] Each case was sequentially allocated based on the age at the time of registration, the egg white-specific IgE antibody titer before immunotherapy, and the reactive dose in the positive egg white-OFC before OIT. The allocation probabilities were set at 0.7 versus 0.3 to correct the unbalanced background factors between groups. When the allocation probability is not extreme (e.g., 0.9), the distribution of background factors could possibly be different between two groups. However, we did not set extreme allocation probabilities as we aimed to emphasize the randomization component of balancing unknown background factors.

OIT was performed using egg white boiled at 100 degrees for 20 min. The starting dose was 0.5 g, 1 g, or 2 g, and it was determined based on the reactive dose and maximum severity scores of entry OFC before OIT. The patients with a maximum severity score of 1 were started at 1/2 of the reactive dose of entry OFC, a maximum severity score of 2 started at 1/4 (rounded down to the nearest decimal point), and a maximum severity score of 3 started at 1/10.

The participants ingested the starting dose at the hospital and were checked for symptoms. All participants were instructed to consume the allergen twice per week. As a compliance indicator, we considered compliance to have been maintained if it was between 36 and 72 total intakes during the 6-month OIT period (an average time 1.5 to 3.5 per week). The intake schedule is supposed to increase the dose at home by 20% per week from the starting dos up to the target dose (**Table S1**). If symptoms occur, medications at home are used or the emergency department is visited, depending on the severity of the symptoms induced at home.

Ingestion of allergens should be discontinued if severe symptoms are observed. If there are moderate symptoms, the dose is reduced to the level before the symptom and the same dose is sustained for at least one month. In case of mild symptoms including throat discomfort or mild perioral redness, the dose is reduced to the level before the symptom and the same dose is sustained for one week. In the patient diary, parents were asked to record intake status and symptoms induced at home. Intake status was evaluated at monthly outpatient visits.

After six months of OIT, boiled egg-white OFC was performed after a one-week elimination period. During the OFC, 1, 2, 5, 10, and 20 g of boiled egg white was consumed every 20 min according to the method specified in the JPGFA 2014.[10]

An egg-white skin-prick test was performed, and blood samples were collected from all the patients before and after OIT. Antigen-specific IgE antibody titers were measured by blood sampling.

Outcome measures

The primary endpoint was the number of patients with a negative result from the egg OFC after 6 months of OIT. If the number of participants with negative results on the OFC was less than 30% (six participants) in both groups, the difference was considered not significant.

The secondary endpoint was safety. We investigated the symptoms associated with ingestion at home during the OIT period, the frequency of epinephrine use, and emergency department visits. The severity of the provoked symptoms was judged using the anaphylaxis grading scale.[10] Induced symptoms at home were recorded in the intake diary by the legal guardians or the patients. The frequency and intensity of the induced symptoms at home were assessed based on the entries in the intake diary. The intensity of induced symptoms was categorized according to anaphylaxis grading scales, including mild, moderate and severe.[13]

Egg white- and ovomucoid-specific IgE titers (Thermo Fisher Scientific, Phadia, Uppsala, Sweden) were measured in blood samples collected before the start and at the end of OIT, and the levels in the two groups were compared. Similarly, a skin-prick test was performed using a bifurcated needle® (Tokyo MI Commerce, Tokyo, Japan) with positive (histamine dihydrochloride, 10 mg/mL) and negative (saline) controls as well as the egg white-prick solution® (Torii Pharmaceutical Co., Tokyo, Japan). The test result was considered positive when the wheal diameter was > 3 mm from that of the negative control. However, the flare diameter was not considered in this study. All assessments were performed according to the JPGFA, 2014.[10]

Statistical analysis

Both intent-to-treat and per-protocol analyses were performed. The Fisher's exact test and chi-square test were used for a two-group comparison of categorical variables, such as sex, presence or absence of comorbid allergic disease, symptom details, and presence or absence of drug treatment. Results were considered statistically significant with two-tailed p-values < 0.05. IBM SPSS Statistics version 22 (IBM, Armonk, NY, USA) was used for all the statistical analyses.

Results

Patient characteristics

Eighty-four children with egg allergy were recruited for this study, and 52 children agreed to participate. The data management center in Osaka Habikino Medical Center randomly assigned participants in a 1:1 ratio to the L-D (n = 23) and H-D (n = 29) groups. There was no intergroup difference in baseline characteristics (**Table 1**). Baselines of egg white- and Ovomucoid-specific IgE levels were not significantly different between the two groups (p = 0.192, egg white-and p = 0.092, ovomucoid-specific IgE levels, **Table 1**).

Table 1. Patients' profiles.

	L-D group (n = 23)	H-D group (n = 29)	$p^{‡}$
Age, years, median (range)[†]	5 (3–12)	6 (3–15)	0.160
Sex (n, male)	19	20	0.749
Reactive dose of EW challenge test before OIT, g, median (range)[†]	2 (1–20)	1 (1–10)	0.961
EW-specific IgE, U_A/mL, median (range)	29.55 (2.89–100)	15.70 (0.69–100)	0.192
Ovomucoid-specific IgE, U_A/mL, median (range)	19.05 (1.49–100)	11.40 (0.34–58.5)	0.092
Other allergic diseases (%)			
Atopic dermatitis	13 (57)	15 (52)	0.785
Bronchial asthma	4 (17)	10 (35)	0.217
Allergic rhinitis	4 (17)	6 (21)	1.000
Allergic conjunctivitis	2 (9)	2 (7)	1.000

[†]Values are displayed as the median and range.
[‡]Statistically significant differences were assessed using the chi-square test or the Mann–Whitney U test in each group.
p < 0.05 was considered statistically significant. The median reactive dose in the boiled EW challenge test before OIT did not differ significantly between the two groups.
Abbreviations: OIT, oral immunotherapy; EW, egg white; L-D, low-dose; H-D: high-dose;

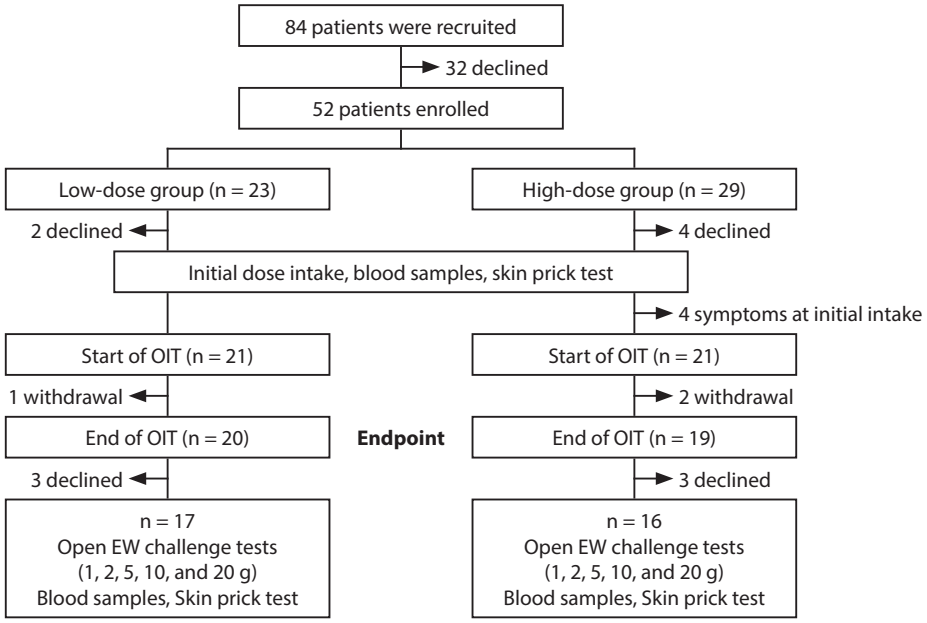

Figure 1. Study design.
Among the 52 patients who were enrolled in this study, 17 patients in each group completed the OIT.
OIT: oral immunotherapy; EW: egg-white;

After the assignment, six patients withdrew their consent before commencing the first OIT intake (n = 2, L-D group and n = 4, H-D group; **Figure 1**). Four patients in the H-D group, OIT could not be started due to symptoms following the initial intake. One patient in the L-D group discontinued the OIT due to anaphylaxis, whereas two patients from the H-D group did not wish to continue OIT, thereby withdrawing from the study. In total, 39 patients (n = 19, H-D group and n = 20, L-D group) completed the 6-month OIT, but six (n = 3, H-D group and n = 3, L-D group) declined consent for exit OFC. In the per-protocol analysis, we compared 16 (H-D group) and 17 (L-D group) patients who underwent OFC and examination.

The median starting doses in the L-D and H-D groups were 0.5 g and 1 g, respectively (p = 0.488; **Tables S2 and S3**). The median intake doses in the L-D and H-D groups were at the end of the OIT in the L-D and H-D groups were 2 and 9 g, respectively (p < 0.0001; **Tables S2 and S3**). In the L-D and H-D groups, 3 (18%, 3/17) and 13 (81%, 13/16) patients, respectively, were unable to reach the maximum target dose due to induced symptoms. In contrast, one participant in the L-D group increased the OIT dose to 3 g, regardless of the instruction to only consume up to 2 g.

Compliance rate

The median total intake times during OIT were 48 times (range 25–141) in the H-D group and 47 times (range 32–143) in the L-D group, with no significant difference (p = 0.736). Compliance was considered good if the total intake was 36 ≥ 72 times during OIT (an average time 1.5 to 3.5 per week).; 10 out of 16 (63%) had good compliance in the H-D group and 13 out of 17 (77%) had good compliance in the L-D group. The number of cases with a total intake less than 36 times was 2 patients in the L-D group and 3 patients in the H-D group; conversely, 2 patients in both groups had a total intake higher than 72 times.

OFC results after 6 months of OIT

In total, three (L-D, 3/17, 18%; H-D, 3/16, 19%) patients in each group tested negative for an OFC performed with a reactive dose of 20 g (p = 1.000; **Tables S1 and S2**). There was no significant intergroup difference at the median final OFC dose of 10 g after 6 months (range, 2–20 g; p = 0.800). The reactive OFC dose after OIT improved significantly in both groups compared to that before the OIT (L-D and H-D groups, p = 0.002 for both; **Figure 2**).

Egg white- and ovomucoid-specific IgE levels and egg white skin-prick test after 6-month OIT

The egg white- and ovomucoid-specific IgE levels after OIT were significantly lower than those before the OIT in both groups (p < 0.001, L-D and p = 0.002, H-D group, **Tables 2, S2, and S3**); however, wheal diameter from the egg-white skin-prick test after OIT were not significantly lower (p = 0.059, L-D and p = 0.131, H-D group, **Table 2**).

Adverse events according to OIT

Among the participants who completed the OIT, the incidence of adverse events was 5.6% (52/933) and 5.7% (49/873) in the L-D and H-D groups, respectively. No serious adverse events occurred. Most symptoms were mild in both groups (50/52 in the L-D group and 45/49 in the H-D group; **Table 3**). However, one patient in the L-D group developed anaphylaxis and was administered epinephrine during OIT; hence, the patient discontinued OIT.

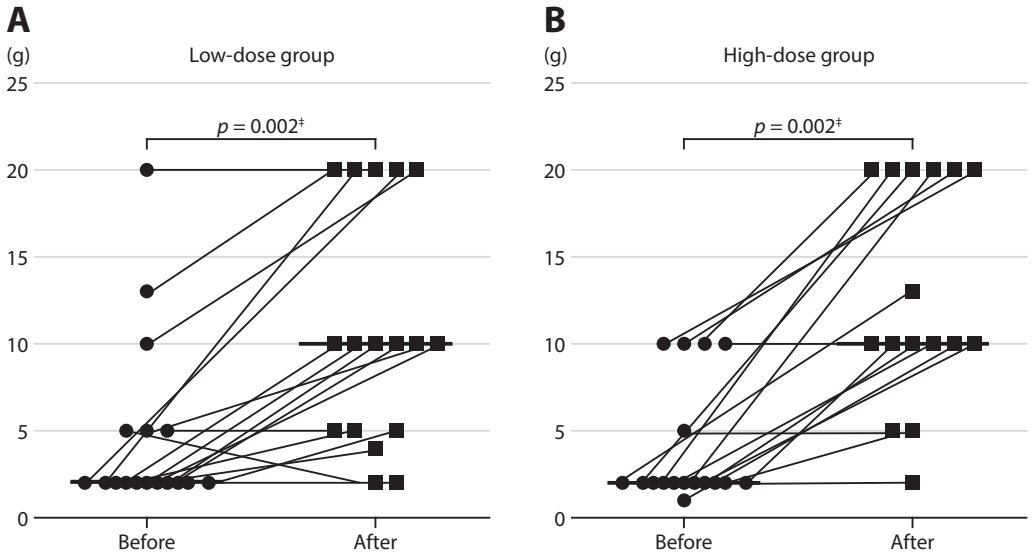

Figure 2. The reactive dose of the boiled egg-white in the OFC test before and after the OIT.
The median final OFC dose after OIT was 10 g (range 2–20 g) in both the study groups. There was no significant intergroup difference in the OFC dose ($p = 0.800$).
‡Statistically significant differences were assessed using the Wilcoxon signed rank test. Statistical significance was set at $p < 0.05$.
OIT: oral immunotherapy; OFC: oral food challenge.

Table 2. Laboratory data and results of the EW skin-prick test before and after OIT.†

	L-D group (n = 17)		p‡	H-D group (n = 16)		p‡
	Before	After		Before	After	
EW-specific IgE, U_A/mL, median (range)	29.60 (2.89–100)	22.00 (2.71–100)	< 0.001	15.85 (4.02–76.0)	14.94 (4.09–75.8)	0.004
Ovomucoid-specific IgE, U_A/mL, median (range)	19.90 (1.49–100)	15.30 (1.84–100)	< 0.001	11.20 (1.40–58.5)	9.30 (0.76–42.2)	0.002
EW skin-prick test, mm, median (range)	11.8 (3–25)	9.5 (0–23.5)	0.059	12.5 (8–18.5)	9.5 (6–14.5)	0.131

†Values are displayed as medians and ranges.
‡Statistically significant differences were assessed using Wilcoxon signed rank test for each group.
Statistical significance was set at $p < 0.05$.
Abbreviations: OIT, oral immunotherapy; EW, egg-white; L-D, low-dose; H-D, high-dose;

Table 3. Adverse events at home.

	L-D group (n = 17)	H-D group (n = 16)	p-value‡
Number of children who developed adverse events	9/17 (52.9)	10/16 (62.5)	1.000
Total intake events (n)	933	873	
Total number of allergic symptoms (%)	52/933 (5.6)	49/873 (5.7)	1.000
Mild	50/933 (5.4)	45/873 (5.2)	0.916
Moderate	2/933 (0.2)	4/873 (0.5)	0.438
Severe	0/933 (0)	0/873 (0)	-
Symptom details (including overlapping) (%)			
Skin	9/933 (1.0)	22/873 (2.5)	0.017
Gastrointestinal tract (including the oral cavity)	49/933 (5.3)	29/873 (3.3)	0.049
Respiratory tract	2/933(0.2)	4/873 (0.5)	0.438
Cardiovascular	0/933(0)	0/873 (0)	-
Neurological	0/933 (0)	0/873 (0)	-

Table 3. (Continued)

	L-D group (n = 17)	H-D group (n = 16)	*p*-value‡
Total number of medications, n (%)			
Oral antihistamine	7/933 (0.7)	13/873 (1.5)	0.177
Bronchodilator	2/933 (0.2)	6/873 (0.7)	0.031
Epinephrine	0/933 (0)	0/873 (0)	-
Admission	0/933 (0)	0/873 (0)	-

‡Statistically significant differences were assessed using the chi-square test.
Statistical significance was set at $p < 0.05$.
The number of children who developed adverse events did not differ significantly. The majority of induced symptoms were mild; no severe symptoms were reported in anyone who completed OIT. However, one patient in the L-D group discontinued OIT due to anaphylaxis.
Abbreviations: L-D, low-dose; H-D, high-dose;

Discussion

In this randomized trial of OIT for egg allergy wherein the effectiveness and safety of the maintenance, low, and high doses were examined, the proportion of subjects passing the exit OFC to 20 g EW and the ED upon exit OFC were comparable between the LD and HD groups. The threshold increase effect was also considered in both groups.

The effects of low-dose OIT have been previously reported. Yanagida et al. evaluated a low-dose OIT that increased the amount to 1/32 heated whole egg (194 mg of chicken egg protein) for patients with hen's egg allergy and found that the percentages of sustained unresponsiveness to 1/32 of the whole egg after 12 months were 71% and 0% in the OIT and control groups, respectively ($p < 0.001$).[14] We previously reported the effect of low-dose OIT with low-allergen egg-containing cookies in severe hen's egg allergy. The thresholds before and after OIT improved significantly in the OIT group ($p = 0.027$).[8]

The effect in low-dose OIT was not inferior to that in the high-dose OIT. In our previous study of low-dose OIT for milk allergy, there was no significant difference in reactive OFC dose between the low-dose and high-dose groups ($p = 0.767$).[9] In the present study, there was a significant decrease in the egg-white- and ovomucoid-specific IgE antibody titers after OIT in both groups (**Table 2**). In addition, the immunological changes were considered in the H-D group and the L-D group. Kulis et al. reported that peanut OIT in the low-dose group decreased responses to cytokines, such as IL-5, IL-13, and IL-9, and basophil activation, as well as in the H-D group.[15]

There was no difference in the frequency of induced symptoms between the two groups, with many symptoms being mild in both groups. However, one patient in the L-D group dropped out because of severe symptoms. We consider OIT to have a risk of induced symptoms. However, there was no difference in induced symptoms due to the maintenance dose. Furthermore, in a previous milk OIT study, the low-dose OIT had fewer severe symptoms than high-dose OIT.[9]

The reactive dose of OFC after OIT did not differ significantly between the two groups; It is unclear whether the same threshold-increasing effect can be observed even if the maximum maintenance dose of OIT is less than 2 g. In an OIT mouse model of hen's egg allergy, the threshold-elevating effect was dependent on the amount of allergen that was ingested.[16]

The limitations of this study include the fact that the study was not a double-blind placebo-controlled trial and had a small, single-center sample. Moreover, sustained unresponsiveness to OFCs after the removal period was not confirmed in this study. The removal period before the exit OFC in the study was short (1 week).

At 6 months, the difference in the number of participants with a negative OFC result, which was the primary endpoint, was less than 30%. Therefore, L-D OIT was not inferior to the H-D OIT. However, the number of participants who had a negative OFC result was lower than expected. It is possible that the 6-month period for confirming the primary evaluation was too short. Furthermore, seven patients in the L-D group and one in the H-D group dropped out because of symptoms or low adherence, possibly due to a dislike for the taste of hard-boiled eggs and the long cooking time. Six people withdrew their consent. Consequently, the number of participants who completed the OIT protocol and underwent an OFC was smaller than the expected sample size. Therefore, it is necessary to develop foods that can facilitate OIT and safer protocols.

Conclusions

Our results revealed that OIT for egg allergy under the low maintenance dose was not inferior to that under the high maintenance dose based on the threshold increase effect. Thus, low-dose OIT could be considered for treatment of hen's egg allergy.

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Conflict of interest

The authors have no conflict of interest to declare.

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Author Contributions

- Yuri Takaoka, Junko Kumon, Tomohiro Yamaguchi, Rumi Ueno, Tamana Nakano, Yohei Fukasawa, Yuki Tsurinaga, Amane Shigekawa, Yukinori Yoshida, Satoru Doi, and Makoto Kameda diagnosed and treated children with allergies and recruited the participants.
- Yoichi M. Ito provided the allocation software and calculated the sample size.
- Yuri Takaoaka and Makoto Kameda designed this study.
- Yuri Takaoaka drafted the manuscript.
- All authors have read and approved the final manuscript.

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Supplemental material

Table S1. Schedule of OIT intake dose.

Week**	Schedule of intake dose* (g)					
	H-D group starting dose (g)			L-D group starting dose (g)		
	0.5 g	1g	2g	0.5 g	1g	2g
1	0.5	1	2	0.5	1	2
2	0.5	1	2	0.5	1	2
3	0.5	1	3	0.5	1	2
4	0.5	1	3	0.5	1	2
5	1	2	4	1	2	2
6	1	2	4	1	2	2
7	1	3	5	1	2	2
8	1	3	6	1	2	2
9	2	4	7	2	2	2
10	2	4	8	2	2	2
11	3	5	9	2	2	2
12	3	6	10	2	2	2
13	4	7	12	2	2	2
14	4	8	14	2	2	2
15	5	9	17	2	2	2
16	6	10	20	2	2	2
17	7	12	20	2	2	2
18	8	14	20	2	2	2
19	9	17	20	2	2	2
20	10	20	20	2	2	2
21	12	20	20	2	2	2
22	14	20	20	2	2	2
23	17	20	20	2	2	2
24	20	20	20	2	2	2

*weight of boiled egg white,
**weeks since starting OIT, Ingestion was started from 1 week.
L-D, low-dose; H-D, high-dose;

Table S2. Age, sex, final dose, and symptom scores for the open egg white challenge tests before and after OIT in the high-dose group

Patient No	Age (years)	Sex	Before			OIT		After		
			EW-sIgE (U_A/mL)	OFC		starting dose of OIT (g)	intake dose at th e nd of OIT(g)	EW-sIgE (U_A/mL)	OFC	
				Final dose (g)	Symptom scores †(according to Ref 8)				Final dose (g)	Symptom scores †(according to Ref 8)
1	8	M	66.00	2	G(2)	0.5	13	32.40	20	G(2)
2	3	M	76.00	10	S(2)	2	16	75.80	20	S(1)
3	5	M	6.45	2	R(2)	0.5	20	4.09	20	G(2)
4	8	M	16.00	2	S(2)R(2)	0.5	5	14.50	5	S(2)R(2)
5	8	M	15.40	2	G(2)N(2)	0.5	20	19.70	20	0
6	7	F	32.30	2	G(2)	0.5	17	15.90	10	G(2)
7	4	F	19.20	10	G(2)	1	2	15.40	20	0
8	6	M	54.10	2	R(2)G(2)	1	7	60.70	13	0
9	15	M	15.10	2	S(2)G(2)	2	8	12.40	10	G(2)
10	3	M	16.90	2	S(2)	0.5	6	12.60	10	S(2)
11	7	F	4.02	10	S(2)	2	20	4.42	20	0
12	5	M	15.70	10	S(1)G(2)	0.5	20	5.64	10	G(2)
13	9	M	13.70	2	G(2)	1	1	14.20	10	R(2)G(3)
14	4	F	13.60	2	S(1)	1	2	18.60	2	R(2)
15	10	M	16.80	1	G(2)	1	4	17.20	10	G(2)
16	6	F	6.75	5	R(2)	1	9	4.95	5	S(1)

Patients No. 8 refused the intake of the 20 g dose for the OFC after OIT, and the final dose was 13 g.
†The severity of the symptoms exhibited in response to the oral boiled egg-white challenge test was determined according to Sampson's anaphylactic grade, which is recommended in the Japanese Pediatric Guideline for Food Allergy, 2014.
OIT, oral immunotherapy; OFC, oral food challenge; M: male; F: female;

Table S3. Age, sex, final dose, and symptom scores in the open egg white challenge tests before and after OIT in the low-dose group

Patient No	Age (years)	Sex	Before			OIT		After		
			EW-sIgE (U_A/mL)	OFC		starting dose of OIT (g)	intake dose at th e nd of OIT(g)	EW-sIgE (U_A/mL)	OFC	
				Final dose (g)	Symptom scores †(according to Ref 8)				Final dose (g)	Symptom scores †(according to Ref 8)
1	9	M	5.03	13	S(1) G(2)	2	2	3.68	20	0
2	7	F	83.70	2	G(2)	0.5	1	63.50	4	G(2)
3	11	M	20.00	5	S(2)R(3)N(3)	0.5	2	19.80	2	S(1)G(2)
4	6	M	8.90	2	S(2)R(2)	0.5	2	13.70	10	S(1)R(3)
5	3	F	17.30	2	R(2)	0.5	2	16.80	20	R(2)
6	3	M	100.00	2	R(2) G(3)	0.5	0.6	100.00	5	R(2)
7	3	M	43.20	2	R(2)G(2)	0.5	2	25.30	20	0
8	5	M	59.70	2	S(2)G(2)	0.5	2	58.10	10	0
9	4	M	8.38	10	S(2)	2	2	4.94	20	0
10	5	F	69.90	2	S(1)	0.5	2	62.00	2	S(1)

Table S3. (Continued)

Patient No	Age (years)	Sex	Before			OIT		After		
			EW-sIgE (U_A/mL)	OFC		starting dose of OIT (g)	intake dose at th e nd of OIT(g)	EW-sIgE (U_A/mL)	OFC	
				Final dose (g)	Symptom scores †(according to Ref 8)				Final dose (g)	Symptom scores †(according to Ref 8)
11	3	M	29.60	20	G(3)	2	2	15.80	20	S(2)R(2)G(2)
12	4	M	100.00	2	G(2)	0.5	1	100.00	10	G(2)
13	4	M	41.00	5	G(2)	1	2	22.00	10	0
14	11	F	29.50	2	G(2)	0.5	2	40.40	10	G(2)
15	6	M	100.00	2	R(2)	0.5	3	91.70	5	R(3)G(2)
16	5	M	2.8	2	S(1)	1	2	2.71	10	S(2)R(2)G(2)
17	4	M	22.90	5	S(2)R(2)	2	2	17.40	5	G(2)N(2)

Patient No. 8 and 13 refused the intake of the 20 g dose during the OFC after OIT. The final dose for these patients was 10 g.
†The severity of the symptoms exhibited in response to the oral boiled egg-white challenge test was determined according to Sampson's anaphylactic grade, which is recommended in the Japanese Pediatric Guideline for Food Allergy, 2014.
OIT, oral immunotherapy; OFC, oral food challenge; M: male; F: female;