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ORIGINAL ARTICLE

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Low-dose oral immunotherapy for children with anaphylactic peanut allergy in Japan

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Abstract

Background: Oral immunotherapy (OIT) is a promising treatment for persons with allergy; however, it can also cause adverse allergic reactions. In this study, we investigated the efficacy of low-dose OIT for anaphylactic peanut allergy.

Methods: Twenty-four children (median age, 9.6 years) with anaphylaxis to peanuts were hospitalized for 5 days and then gradually fed increasing amounts of peanut powder up to 133 mg/day. One year later, they underwent an oral food challenge after 2 weeks of peanut avoidance. Those who were asymptomatic after ingesting 795 mg of peanut protein were defined as having achieved sustained unresponsiveness. We measured peanut- and Ara h2-specific immunoglobulin (Ig) E, IgG, and IgG4 levels at 0, 1, 3, 6, and 12 months in the OIT group and at 0 and 12 months in the control group.

Results: At baseline, all children in the OIT group and 8 in the control group had a history of anaphylaxis. The median peanut-/Ara h2-specific IgE levels in the OIT and control groups were 55.4/48.6 and 58.2/38.1 kUa/L, respectively. One year later, 8 (33.3%) children in the OIT group exhibited sustained unresponsiveness, while none in the control group did. In the OIT group, the median peanut-specific IgE levels significantly increased to 194.0 kUa/L, after 1 month and then significantly decreased to 57.5 kUa/L at 12 months. Meanwhile, the median peanut- and Ara h2-specific IgG and IgG4 levels increased significantly after 1 month.

Conclusion: Low-dose OIT induces immunological changes and has the capability of achieving sustained unresponsiveness in children with peanut anaphylaxis.

KEYWORDS

anaphylaxis, desensitization, oral immunotherapy, peanut, sustained unresponsiveness

1 | INTRODUCTION

Peanut allergy is a common disease[1-3] and is one of the major causes of anaphylaxis.[4] In Japan, peanuts account for 4.6% of anaphylactic food reactions.[5] In some persons, even a trace amount of peanut ingestion can lead to anaphylaxis.[6] Annually, 12% of Canadians with peanut allergy accidentally ingest peanuts.[7] Considering that peanuts are among the most common food ingredients, the quality of life of such patients would improve if they were able to consume peanuts in small amounts.[8,9] In general, only 20% of children with peanut allergy develop tolerance[10,11]; hence, most of these individuals remain at constant risk of anaphylaxis from accidental ingestion.

Although oral immunotherapy (OIT) has been attracting attention as treatment for peanut allergy, adverse clinical events, including severe anaphylactic symptoms, such as shortness of breath and fainting, may develop during OIT. Moreover, studies regarding

OIT among patients with anaphylactic food allergy are sparse.[12-14] We previously reported the efficacy of low-dose OIT for patients who had anaphylactic reactions to hen's egg and cow's milk.[15,16] Additionally, low-dose peanut OIT was previously investigated by Vickery et al; however, they excluded patients who developed severe anaphylaxis from their trial.[17] Therefore, data on the efficacy of low-dose peanut OIT in children with anaphylaxis are limited.

In this study, we investigated the effects of OIT in children who are anaphylactic to peanuts, using a lower target dose than is conventionally used.

2 | METHODS

2.1 | Study design

This study was a prospective clinical trial performed at Sagamihara National Hospital between July 2013 and March 2016 (UMIN000011202). Neither the OIT group nor the historical control group was randomly selected. The historical control group was selected from patients who were matched for OIT patients. They did not ingest placebo powder. The OIT group was enrolled in an open-label study.

2.2 | Participants

Participants were 5- to 18-year-old individuals with a history of anaphylaxis or high levels of peanut-specific immunoglobulin (Ig) E (>50 kUa/L).

Participants who developed objective symptoms during an oral food challenge (OFC) of 133-mg peanut protein were included in the OIT group. Exclusion criteria were poorly controlled bronchial asthma, atopic dermatitis, or participation in any other immunotherapy (Figure 1). Patients who had a history of severe peanut anaphylaxis or those with high levels of specific IgE were not excluded.

Because OIT is performed at many facilities in Japan,[18] patients and their guardians visited our hospital expecting to receive this therapy. Therefore, we were unable to designate a strict control group. Instead, we assigned a historical control group for comparing outcomes. For this group, we selected all patients aged 5 to 18 years who presented with objective symptoms during an OFC of 133-mg peanut protein at our hospital between 2013 and 2015 and who completely avoided peanuts before undergoing a second OFC more than 1 year (from 2014 to 2016) after the first OFC (Figure 1).

2.3 | Oral food challenge

We used a pumpkin cake that included 133 mg of peanut protein for the first OFC and 795 mg for the final OFC; recipes are described in Table S1. The quantitative value of peanut protein was assessed using the Kjeldahl method. The pumpkin cake, containing 33.2 mg or 99.8 mg of peanut protein, was offered to the children in 2 consecutive feedings with a 60-minute interval. OFC was regarded as positive when the first objective allergic symptoms were observed. We provided appropriate treatment based on the severity of symptoms according to the Japanese guidelines for food allergy (Table S2).[19,20] Symptom severity was determined based on the organ with the most severe symptoms; the threshold dose was defined as the accumulated dose at the time objective symptoms appeared.

2.4 | Oral immunotherapy protocol

The OIT protocol is illustrated in Figure 2. Patients received 10 mg of loratadine as pre-medication. On the first day, peanut powder at half the threshold dose of the OFC was administered twice daily at 2-hour intervals. The OIT protocol consisted of 8 increments, starting from 8 mg of peanut protein and gradually increasing to 133 mg (Table S3). Patients ingested peanut powder twice daily during the 5 days of hospitalization. If symptoms were mild or non-existent, the next amount was administered the following day. Up to 1 month after discharge, intake was continued at the amount decided at the time of discharge. After 1 month, if asymptomatic intake continued for 5 consecutive days, the intake dose was increased by 1 step. Patients gradually increased the amount of peanut powder up to 133 mg/day (the target dose). To

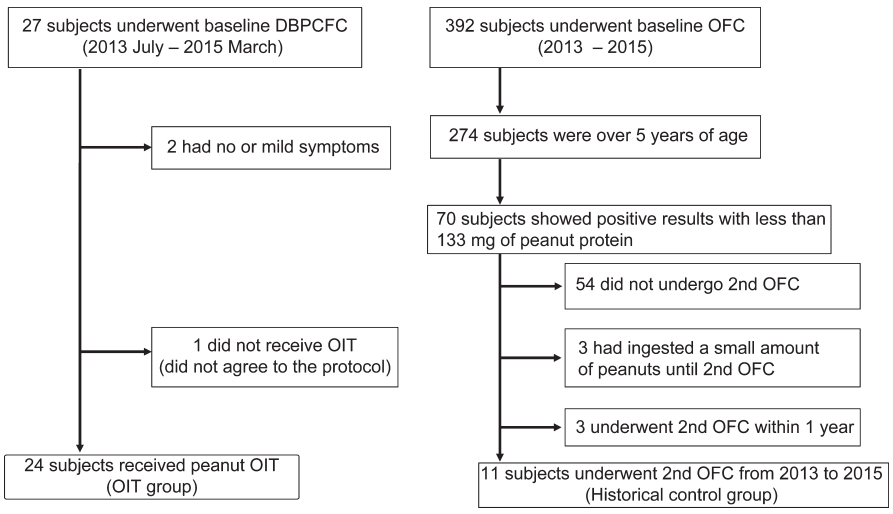

FIGURE 1 Flowchart of participant selection (OIT and historical control groups). DBPCFC, double-blind, placebo-controlled food challenge; OFC, oral food challenge; OIT, oral immunotherapy

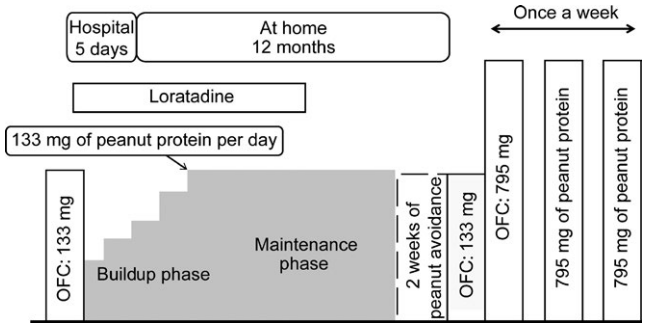

FIGURE 2 OIT protocol. OFC, oral food challenge; OIT, oral immunotherapy

treat adverse reactions, we prescribed 10 mg of epinastine, 1 mg/kg of prednisolone, salbutamol sulfate, and an adrenaline autoinjector (0.15 mg or 0.3 mg) to all patients. Both the children and their guardians were instructed regarding proper use of the drugs; the guardians recorded the presence/absence of symptoms daily. When Grade 1 symptoms appeared, dosing for the next day did not change; when Grade 2 symptoms appeared, dosing was decreased by 1 step; and when Grade 3 symptoms appeared, dosing was decreased by 2 steps. Throughout the study, a direct telephone hotline was available 24 hours a day. Patients took maintenance doses daily after the buildup phase and visited our hospital every 1-3 months. When they were able to consume 133 mg without symptoms for 1 month, the pre-medication was withdrawn. One year after commencing the OIT, patients temporarily discontinued therapy for 2 weeks, after which they underwent a 133-mg and 795-mg OFC on 2 consecutive days. Because we conducted OIT for preventing anaphylaxis, if patients were able to ingest peanut protein after 2 weeks of avoidance, risk of anaphylaxis was considered to have decreased. Indeed, more than half of the patients were able to ingest peanut protein without symptoms. Patients who passed these OFCs were instructed to ingest another 795 mg of peanut protein once a week, and those who did not develop any symptoms 3 months after the OFC were considered to have achieved "sustained unresponsiveness." If patients did not achieve sustained unresponsiveness, we instructed them to ingest 133 mg.

2.5 | Immunological parameters

We measured peanut- and Ara h2-specific IgE, IgG, and IgG4 levels (ImmunoCAP assay system, Thermo Fisher Scientific, Uppsala., Sweden) at 0, 1, 3, 6, and 12 months in the OIT group and at the first and second OFCs in the historical control group.

2.6 | End-points

The primary end-point was the achievement of sustained unresponsiveness after 1 year in the OIT group as compared to the historical control group. The secondary end-points were decreased levels of peanut- and Ara h2-specific IgE, IgG, and IgG4 in both groups.

2.7 | Statistical analysis

The derived values are expressed as median and range. Differences in continuous variables between groups were assessed using Wilcoxon rank-sum tests, while differences in categorical data were examined using the Fisher's exact test. A *P*-value <.05 was considered statistically significant. All analyses were performed using SPSS 24.0 software (IBM Corp., Armonk, NY, USA).

2.8 | Ethical considerations

This study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Sagamihara National Hospital Ethics Committee. The study design and risk of symptoms were fully explained orally and in writing to the patients and their guardians. Informed consent/assent was obtained from all patients and guardians. All data were anonymized prior to analysis.

3 | RESULTS

3.1 | Participant background

Twenty-seven children with peanut anaphylaxis underwent OFC, 25 of whom showed objective symptoms. One child did not consent to participate in the OIT; hence, 24 children (median age, 9.6 years) underwent peanut OIT (Figure 1). The historical control group consisted of 10 children (median age, 7.6 years). In the OIT group, all children had a history of anaphylaxis to peanuts; the median number of anaphylactic episodes was 2. The median peanut-specific IgE level was 55.4 (2.3-400) kUa/L, while the Ara h2-specific IgE level was 48.6 (1.5-303) kUa/L. Prior to OIT, the mean threshold that induced objective symptoms was 87 mg. The proportion of children who had a history of anaphylaxis was higher in the OIT group than in the historical control group (100% vs 80%) (*P* = .02) (Table 1).

3.2 | Clinical outcomes

In the OIT group, all children completed the protocol, and 22 (92%) achieved desensitization within 1 year (median 3 months, range 1-5 months). After 1 year, 16 children (67%) passed the 133-mg OFC, and 14 (58%) passed the 795-mg OFC. Only 1 child (10%) in the historical control group passed the 133-mg OFC (*P* = .006). Ultimately, 8 children (33%) in the OIT group achieved sustained unresponsiveness, whereas no child in the historical control group was able to consume the 795-mg peanut protein (*P* = .03) (Table 2).

3.3 | Adverse reactions and treatments

During admission, 79 of the 119 total doses (66.4%) resulted in allergic reactions; however, no severe symptoms developed. A total of 26% of adverse reactions required treatment, and no child received intramuscular adrenaline during admission.

TABLE 1 Patients' profiles

	OIT group (n = 24)	Historical control group (n = 10)	*P*-value
Age (y)	9.6 (6.1–16.2)	7.6 (5.7-12.7)	ns**
Male, n (%)	18 (75.0%)	7 (70.0%)	ns*
History of anaphylaxis due to peanut, n (%)	24 (100.0%)	8 (80.0%)	.02*
Number of incidents of anaphylaxis	2 (1–3)	1 (0–3)	ns**
Complications			
BA, current, n (%)	8 (33.3%)	4 (40.0%)	ns*
AD, current, n (%)	11 (45.8%)	4 (40.0%)	ns*
AR, current, n (%)	16 (66.7%)	5 (50.0%)	ns*
Severity of symptoms during first OFC			
Mild	1	1	ns*
Moderate	22	7	
Severe	1	2	
Mean threshold of first OFC (mg)	87 (33–133)	98 (33–133)	ns**
Specific IgE			
Peanut (kUa/L)	55.4 (2.3–400)	58.2 (2.8–167)	ns**
Ara h2 (kUa/L)	48.6 (1.5–303)	38.1 (0.05–71.3)	ns**
Specific IgG4			
Peanut (mg/L)	0.43 (0.03–3.95)	0.45 (0.03–2.3)	ns**
Ara h2 (mg/L)	0.23 (0.03–2.9)	0.15 (0.03–1.25)	ns**
Skin prick test			
Wheal (mm)	12 (6–23)	15 (10–21)	ns**
Erythema (mm)	24 (11–48)	30 (18–37)	ns**

AD, atopic dermatitis; AR, allergic rhinitis; BA: bronchial asthma; ns, not significant; OFC, oral food challenge; OIT, oral immunotherapy.
Values with parentheses denote median (range).
*Fisher's exact test.
**Wilcoxon's rank-sum test.

TABLE 2 Results following the 12-month treatment or elimination period

	OIT group (n = 24)	Historical control group (n = 10)	*P*-value
Desensitization to 133 mg	22 (91.7%)	1 (10%)	<.0001
Passed 133-mg OFC	16 (66.7%)	1 (10%)	.006
Passed 795-mg OFC	14 (58.3%)	0 (0%)	.001
Sustained unresponsiveness to 795-mg peanut protein	8 (33.3%)	0 (0%)	.03

OFC, oral food challenge; OIT, oral immunotherapy.
P-values were calculated using Fisher's exact test.

During the home dosing phase, total doses resulted in symptoms in 9.1% of the participants. Meanwhile, severe symptoms occurred in 0.01%. One child received intramuscular adrenaline at home due to continuous repetitive coughing after intake (Table 3). Moreover, there was no accidental peanut exposure in the historical control group during the study period.

3.4 | Laboratory data

The median peanut- and Ara h2-specific IgE levels significantly increased from baseline to 1 month (194.0 kUa/L, 156.7 kUa/L, respectively) ($P < .001$) and significantly decreased (compared to 1 month) at 3, 6, and 12 months. The median peanut- and Ara h2-specific IgG levels in the OIT group increased significantly from baseline (7.39 mgA/L, 6.94 mgA/L, respectively) to 1 month (36.8 mgA/L, 28.6 mgA/L, respectively) ($P < .001$). Similarly, peanut- and Ara h2-specific IgG4 increased significantly from baseline (0.43 mgA/L, 0.23 mgA/L, respectively) to 1 month (2.3 mgA/L, 1.8 mgA/L, respectively) ($P < .001$) (Figure 3). No significant changes were observed in the historical control group (Figure S1).

TABLE 3 Adverse allergic reactions during the oral immunotherapy protocol

Adverse reactions and treatment	Hospital	Home
Total number of intakes	119	8209
Total number of adverse reactions, n (%)	79 (66.4%)	744 (9.1%)
Mild, n (%)	46 (38.7%)	608 (7.4%)
Moderate, n (%)	33 (27.7%)	123 (1.5%)
Severe, n (%)	0 (0.0%)	1 (0.01%)
Gastrointestinal symptoms, n (%)	34 (28.6%)	744 (9.1%)
Mucosal symptoms, n (%)	29 (24.4%)	354 (4.3%)
Cutaneous symptoms, n (%)	18 (15.1%)	140 (1.7%)
Respiratory symptoms, n (%)	18 (15.1%)	81 (1.0%)
Cardiovascular symptoms, n (%)	0 (0.0%)	0 (0.0%)
Treatment		
Any treatment, n (%)	31 (26.1%)	174 (2.1%)
Antihistamine, n (%)	27 (22.7%)	166 (2.0%)
Corticosteroid, n (%)	6 (5.0%)	18 (0.2%)
β_2 inhalation, n (%)	10 (8.4%)	10 (0.1%)
Adrenaline, n (%)	0 (0.0%)	1 (0.01%)

OIT, oral immunotherapy.

3.5 | Predictor of sustained unresponsiveness

We compared the baseline characteristics of the OIT group participants who achieved sustained unresponsiveness with characteristics of the participants who did not achieve sustained unresponsiveness. At baseline, Ara h2-specific IgE level was 29.9 kUa/L in the sustained unresponsiveness group and 71.1 kUa/L in the allergic group. Ara h2-specific IgE level was the only predictive factor for the achievement of sustained unresponsiveness (Table S4).

4 | DISCUSSION

To our knowledge, this is the first study to show that low-dose OIT induces immunological changes and sustained unresponsiveness in patients with peanut anaphylaxis. Although some trials have demonstrated the efficacy of peanut OIT, knowledge regarding OIT for patients with anaphylactic peanut allergy is sparse.[12-15,21] Here, all patients had a history of previous anaphylaxis, and peanut-specific IgE levels were high (median, 55.4 kUa/L), factors which may lower the efficacy of conventional OIT.[21,22]

The efficacy and safety of low-dose OIT for those allergic to hen's egg, cow's milk, and peanut have recently been reported.[15-17] The frequency of moderate-to-severe symptoms, including those requiring treatment, was lower with low-dose OIT than with conventional OIT.[23] In terms of low-dose peanut OIT, Vickery et al reported that 85% of patients in their OIT study's low-dose group (300 mg) and 71% in their high-dose group (3000 mg) achieved sustained unresponsiveness.[17] Their data suggested that low-dose peanut OIT may effectively induce sustained unresponsiveness. However, their trial appears to have enrolled patients with relatively mild peanut allergy, as the median peanut-specific IgE was only 14.4 kUa/L and those with severe anaphylaxis were excluded. By contrast, all patients in our study had a history of anaphylaxis as well as high levels of peanut- and Ara h2-specific IgE, and our approach showed marked efficacy of low-dose OIT, as evidenced by 92% of our patients achieving desensitization and 33% achieving sustained unresponsiveness.

With respect to adverse allergic reactions during conventional peanut OIT, Anagnostou et al[12] reported low rates of such incidences in their slow OIT study with a target dose of 800 mg of peanut protein. In their study, allergic reactions ranged from oral itching (6.3%) to wheezing (0.41%); only 1 of their patients self-administered intramuscular adrenaline "twice". However, the frequency of these symptoms tended to be higher in patients from this previous study than those in our study (for whom intake at home was also a therapy component). Additionally, Hofmann et al[13] performed an OIT trial with a maintenance dose of 300 mg of peanut protein. Adrenaline was administered to 4 of their patients (14%) during the initial escalation period and to 2 patients during the home dosing period. In our study, intramuscular adrenaline was never administered at the hospital—only "once" at home. This rate was lower than that of the aforementioned studies, potentially owing to a lower target dose of 133 mg in our trial. Accordingly, these findings indicate that our low-dose OIT protocol is relatively safe.

Previous studies revealed peanut- and Ara h2-specific IgE and IgG4 changes in rush OIT.[21,24] Although the target dose in our study was lower than that in other studies, the levels of peanut- and Ara h2-specific IgE significantly increased after 1 month of treatment and then significantly decreased at 3, 6, and 12 months. Furthermore, peanut- and Ara h2-specific IgG and IgG4 significantly increased after 1 month. To our knowledge, we are the first to report that low-dose peanut OIT induces such immunological changes and that low-dose peanut OIT may be an effective treatment to induce immunological changes and sustained unresponsiveness in children with severe peanut allergy.

A limitation of this study was the differences in characteristics between the participants in the OIT and historical control groups (Table 1). Because patients and their parents expected OIT, we were unable to establish a strict control group. However, all patients in the OIT group had a history of anaphylaxis to peanuts. In general, such patients are unlikely to acquire tolerance.[25,26] Nevertheless, the treatment outcome was better in the OIT group, suggesting that any differences in characteristics had a minimal influence on the outcome. Another limitation is that 2 weeks of avoidance of peanut protein may be insufficient to assess achievement of sustained unresponsiveness.[27] However, the purpose of our study was to prevent anaphylactic symptoms

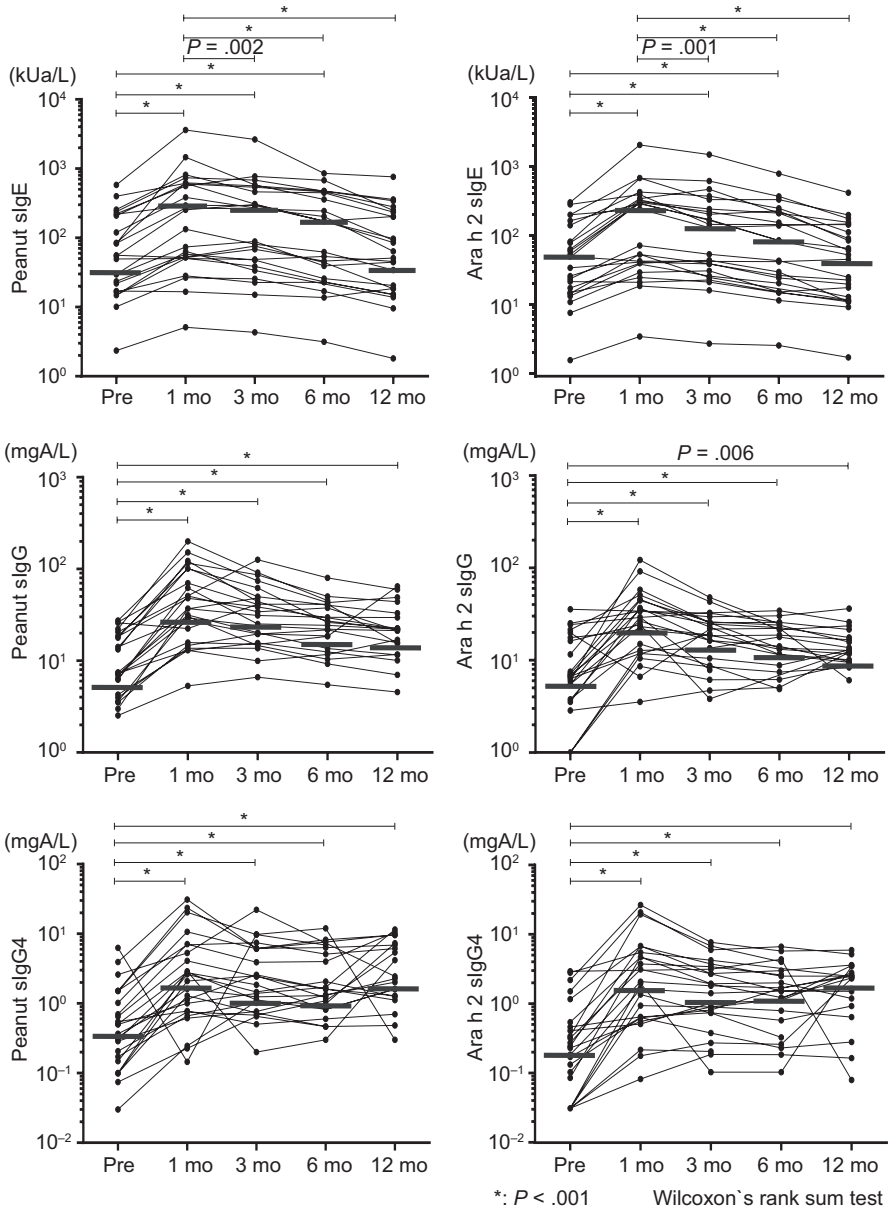

FIGURE 3 Specific IgE, IgG, and IgG4 changes in the OIT group. Peanut- and Ara h2-specific IgE levels significantly increased at 1 month and then significantly decreased. Peanut- and Ara h2-specific IgG and IgG4 levels also increased significantly after 1 month. OIT: oral immunotherapy, sIgE: specific IgE, sIgG: specific IgG, sIgG4: specific IgG4

due to accidental exposure in patients with severe peanut anaphylaxis. If patients were able to ingest peanuts after 2 weeks of complete avoidance, then the risk of anaphylaxis ought to be low in daily life. Additionally, previous studies defined sustained unresponsiveness as passing the OFC after discontinuing OIT; however, such patients were still susceptible to developing allergic symptoms.[28] Therefore, we defined sustained unresponsiveness as both passing the OFC and successfully ingesting peanut protein once a week at home without symptoms. As such, patients were essentially able to consume peanuts in real-life settings. Moreover, a 2-week abstinence period has been used in other OIT trials.[16,29]

Finally, we excluded those with poorly controlled bronchial asthma or atopic dermatitis, because these patients have a high risk of adverse reactions.[29,30] Therefore, these findings may not be applicable to those patients.

In conclusion, as compared to conventional OIT, low-dose OIT more safely induced immunological changes in patients with anaphylaxis to peanuts and appeared to be effective in inducing sustained unresponsiveness.

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CONFLICT OF INTERESTS

Motohiro Ebisawa is on the scientific advisory board of DBV Technologies and received lecturing fees from Pfizer and Siemens. The other authors declare that they have no conflict of interests.

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REFERENCES

1. Grundy J, Matthews S, Bateman B, Dean T, Arshad SH. Rising prevalence of allergy to peanut in children: data from 2 sequential cohorts. *J Allergy Clin Immunol*. 2002;110:784-789.
2. Sicherer SH, Munoz-Furlong A, Godbold JH, Sampson HA. US prevalence of self-reported peanut, tree nut, and sesame allergy: 11-year follow-up. *J Allergy Clin Immunol*. 2010;125:1322-1326.
3. Sicherer SH, Munoz-Furlong A, Sampson HA. Prevalence of peanut and tree nut allergy in the United States determined by means of a random digit dial telephone survey: a 5-year follow-up study. *J Allergy Clin Immunol*. 2003;112:1203-1207.
4. Panesar SS, Javad S, de Silva D, et al. The epidemiology of anaphylaxis in Europe: a systematic review. *Allergy*. 2013;68:1353-1361.
5. Akiyama H, Imai T, Ebisawa M. Japan food allergen labeling regulation–history and evaluation. *Adv Food Nutr Res*. 2011;62:139-171.
6. Wensing M, Penninks AH, Hefle SL, Koppelman SJ, Bruijnzeel-Koomen CA, Knulst AC. The distribution of individual threshold doses eliciting allergic reactions in a population with peanut allergy. *J Allergy Clin Immunol*. 2002;110:915-920.
7. Cherkaoui S, Ben-Shoshan M, Alizadehfar R, et al. Accidental exposures to peanut in a large cohort of Canadian children with peanut allergy. *Clin Transl Allergy*. 2015;5:16.
8. Ward C, Greenhawt M. Differences in caregiver food allergy quality of life between a tertiary care, specialty clinic, and a caregiver reported food allergic populations. *J Allergy Clin Immunol Pract*. 2016;4:257-264.
9. Walkner M, Warren C, Gupta RS. Quality of life in food allergy patients and their families. *Pediatr Clin North Am*. 2015;62:1453-1461.
10. Skolnick HS, Conover-Walker MK, Koerner CB, Sampson HA, Burks W, Wood RA. The natural history of peanut allergy. *J Allergy Clin Immunol*. 2001;107:367-374.
11. Peters RL, Allen KJ, Dharmage SC, et al. Natural history of peanut allergy and predictors of resolution in the first 4 years of life: a population-based assessment. *J Allergy Clin Immunol*. 2015;135:1257-1266. e1-2.
12. Anagnostou K, Islam S, King Y, et al. Assessing the efficacy of oral immunotherapy for the desensitisation of peanut allergy in children (STOP II): a phase 2 randomised controlled trial. *Lancet*. 2014;383:1297-1304.
13. Hofmann AM, Scurlock AM, Jones SM, et al. Safety of a peanut oral immunotherapy protocol in children with peanut allergy. *J Allergy Clin Immunol*. 2009;124:286-291, 91.e1-6.
14. Varshney P, Jones SM, Scurlock AM, et al. A randomized controlled study of peanut oral immunotherapy: clinical desensitization and modulation of the allergic response. *J Allergy Clin Immunol*. 2011;127:654-660.
15. Yanagida N, Sato S, Asaumi T, Okada Y, Ogura K, Ebisawa M. A single-center, case-control study of low-dose-induction oral immunotherapy with cow's milk. *Int Arch Allergy Immunol*. 2015;168:131-137.
16. Yanagida N, Sato S, Asaumi T, Nagakura K, Ogura K, Ebisawa M. Safety and efficacy of low-dose oral immunotherapy for hen's egg allergy in children. *Int Arch Allergy Immunol*. 2016;171:265-268.
17. Vickery BP, Berglund JP, Burk CM, et al. Early oral immunotherapy in peanut-allergic preschool children is safe and highly effective. *J Allergy Clin Immunol*. 2017;139:173-181.
18. Ebisawa M, Nishima S, Ohnishi H, Kondo N. Pediatric allergy and immunology in Japan. *Pediatr Allergy Immunol*. 2013;24:704-714.
19. Ebisawa M, Ito K, Fujisawa T. Japanese guidelines for food allergy 2017. *Allergol Int*. 2017;66:248-264.
20. Yanagida N, Sato S, Asaumi T, Ogura K, Ebisawa M. Risk factors for severe reactions during double-blind placebo-controlled food challenges. *Int Arch Allergy Immunol*. 2017;172:173-182.
21. Vickery BP, Scurlock AM, Kulis M, et al. Sustained unresponsiveness to peanut in subjects who have completed peanut oral immunotherapy. *J Allergy Clin Immunol*. 2014;133:468-475.
22. Anagnostou K, Clark A, King Y, Islam S, Deighton J, Ewan P. Efficacy and safety of high-dose peanut oral immunotherapy with factors predicting outcome. *Clin Exp Allergy*. 2011;41:1273-1281.
23. Yanagida N, Okada Y, Sato S, Ebisawa M. New approach for food allergy management using low-dose oral food challenges and low-dose oral immunotherapies. *Allergol Int*. 2016;65:135-140.
24. Nozawa A, Okamoto Y, Moverare R, Borres MP, Kurihara K. Monitoring Ara h 1, 2 and 3-sIgE and sIgG4 antibodies in peanut allergic children receiving oral rush immunotherapy. *Pediatr Allergy Immunol*. 2014;25:323-328.
25. Sicherer SH, Wood RA, Vickery BP, et al. The natural history of egg allergy in an observational cohort. *J Allergy Clin Immunol*. 2014;133:492-499.
26. Ohtani K, Sato S, Syukuya A, et al. Natural history of immediate-type hen's egg allergy in Japanese children. *Allergol Int*. 2016;65:153-157.
27. Wood RA. Food allergen immunotherapy: current status and prospects for the future. *J Allergy Clin Immunol*. 2016;137:973-982.
28. Keet CA, Seopaul S, Knorr S, Narisety S, Skripak J, Wood RA. Long-term follow-up of oral immunotherapy for cow's milk allergy. *J Allergy Clin Immunol*. 2013;132:737-739.
29. Sato S, Utsunomiya T, Imai T, et al. Wheat oral immunotherapy for wheat-induced anaphylaxis. *J Allergy Clin Immunol*. 2015;136:1131-1133.
30. Pajno GB, Fernandez-Rivas M, Arasi S, et al. EAACI Guidelines on allergen immunotherapy: IgE-mediated food allergy. *Allergy* 2018;73:799-815.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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