

Oral Immunotherapy in Japanese Children with Anaphylactic Peanut Allergy

Ken-ichi Nagakura^{a, b} Sakura Sato^c Noriyuki Yanagida^a Makoto Nishino^a
Tomoyuki Asaumi^a Kiyotake Ogura^a Motohiro Ebisawa^c

^aDepartment of Pediatrics, Sagamihara National Hospital, Sagamihara, Japan; ^bDepartment of Pediatrics, Jikei University School of Medicine, Tokyo, Japan; ^cDepartment of Allergy, Clinical Research Center for Allergy and Rheumatology, Sagamihara National Hospital, Sagamihara, Japan

Keywords

Anaphylaxis · Double-blind placebo-controlled food challenge · Efficacy · Oral immunotherapy · Peanut · Safety · Threshold · Unresponsiveness

Abstract

Background: Reports on oral immunotherapy (OIT) for anaphylactic food allergy are lacking. We investigated the efficacy and safety of peanut OIT for anaphylactic patients. **Methods:** We enrolled 22 peanut anaphylactic patients who underwent OIT between 2011 and 2013, all of whom demonstrated anaphylaxis during a baseline double-blind, placebo-controlled food challenge. After starting in-hospital OIT, participants gradually increased ingestion to 795 mg of peanut protein per day at home and then took a maintenance dose (795 mg) daily. After 3 asymptomatic months, participants underwent an oral food challenge (OFC) of 795 mg after 2 weeks of peanut avoidance to confirm sustained unresponsiveness. The historical control group consisted of 11 patients with anaphylaxis by OFC and underwent the second OFC after 2 years. **Results:** All patients (22/22) achieved desensitization by 8 months after starting OIT and completed the protocol within 2 years. Two years later, 15/22 pa-

tients (68.1%) in the OIT group achieved sustained unresponsiveness, whereas only 2 (18.1%) in the control group passed the second OFC. After 2 years, the median peanut-specific IgE had significantly decreased (from 38.5 to 12.4 kUA/L) in the OIT group, but not in the control group. Median peanut- and Ara h 2-specific IgG4 in the OIT group had significantly increased from baseline after 1 month. The adverse reaction rate per ingestion was 43% in hospital and 5% at home. Three patients received adrenaline at the hospital and 2 at home. **Conclusions:** These data suggest that for patients with peanut anaphylaxis, OIT can increase the threshold and support achieving sustained unresponsiveness with relative safety.

© 2018 S. Karger AG, Basel

Introduction

There have been many reports of a trend toward an increase in the prevalence of peanut allergy in western countries [1, 2]. Peanut anaphylaxis comprise 18% of

Edited by: A.W. Burks, Chapel Hill, NC.

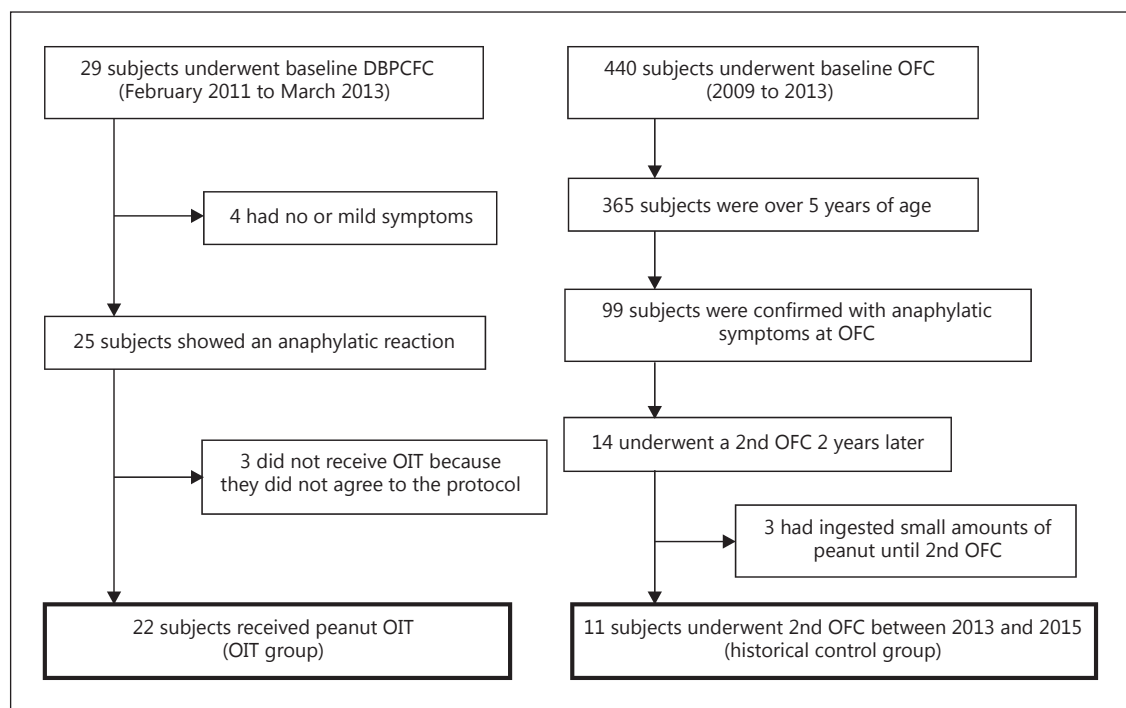


Fig. 1. Study participants: OIT group and historical control group.

food anaphylaxis [3] and 55% of fatalities from food allergies in the United States [4]. On the other hand, in Japan, peanuts account for 4.6% of food anaphylactic antigens [5]. Even a trace amount of peanut ingestion can cause anaphylaxis [6]; the annual rate of accidental ingestion is reported to be 12% among Canadian patients with peanut allergy [7]. Basic management for food allergic patients with a history of anaphylaxis is to avoid causative foods while waiting for natural tolerance acquisition [8]. However, the rate of tolerance acquisition for peanuts is low, reported to be about 20% [9, 10]. Therefore, peanut-allergic patients are always at risk of anaphylaxis from accidental ingestion.

In recent years, oral immunotherapy (OIT) has been attracting attention as a novel treatment approach for food allergy [11]. OIT for peanut-allergic patients induces desensitization in the majority of patients, some of whom achieve sustained unresponsiveness; however, reports for anaphylactic patients are lacking [12–15].

The purpose of this study was to examine the efficacy and safety of OIT for anaphylactic patients to induce desensitization and sustained unresponsiveness to peanut. This is the first report regarding peanut OIT for patients with anaphylactic symptoms.

Methods

Study Design

OIT Group

This study was prospective, a single-center study performed at the Sagami National Hospital. OIT inclusion criteria were age over 5 years and confirmed objective reactions in a double-blind placebo-controlled food challenge (DBPCFC) with 795 mg of peanut protein (3 g of whole peanut) between February 2011 and March 2013. Anaphylaxis was defined by World Allergy Organization guidelines for the assessment and management of anaphylaxis [16, 17]. The exclusion criteria were congenital blood disease, digestive disease, neurological disease requiring treatment, poorly controlled bronchial asthma, atopic dermatitis, or on any other immunotherapy (Fig. 1). We did not exclude patients who had a history of severe peanut anaphylaxis or those with high levels of specific IgE.

Historical Control Group

Because OIT is conducted widely in Japan [18], patients visited our hospital from all over the country hoping to participate in the active group [19]; accordingly, we were unable to include a synchronous control group in the study. Instead, we used a historical control group for comparison. For the historical control group, we selected all patients over 5 years old who had confirmed anaphylactic reactions to an oral food challenge (OFC) with 795 mg of peanut protein at our hospital between 2009 and 2013, who had completely eliminated peanut from their diet, and had undergone a second OFC after more than 2 years. Patients

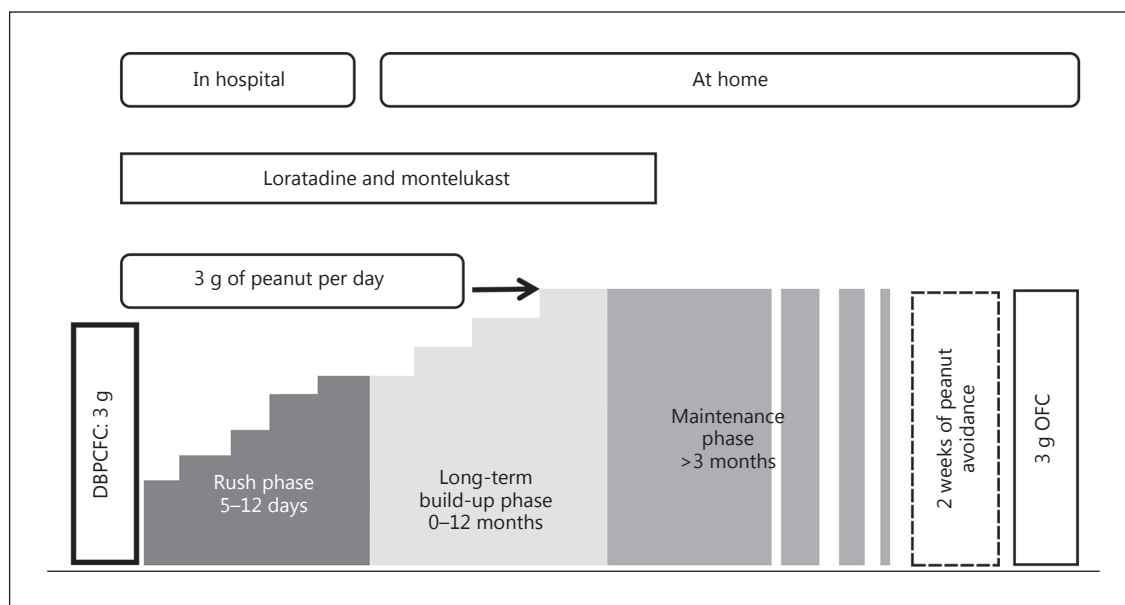


Fig. 2. OIT protocol.

who had been taking a trace amount of peanut before the second OFC or those who had the second OFC within 2 years were excluded (Fig. 1).

DBPCFC

For the DBPCFC, we used peanut powder, with cumulative doses of 795 mg of peanut protein, and we used lactose as a placebo mixed with strawberry puree. We administered peanut powder or placebo in 5 separate portions at 30-min intervals: 33, 66, 133, 199, and 364 mg of peanut protein. We regarded an OFC as positive and the challenges were discontinued when we observed the first objective allergic reaction. Appropriate management, including antihistamine, corticosteroid, β_2 -agonist inhalation, or intramuscular adrenaline, was administered based on the severity of symptoms according to the Japanese guidelines for food allergy (online suppl. Table 1S; for all online suppl. material, see www.karger.com/doi/10.1159/000486310) [20, 21]. The severity of symptoms was based on the organ with the most severe symptoms. The threshold volume was defined as the accumulated dose.

OIT Protocol

The OIT protocol is shown in Figure 2. As premedication, 10 mg of loratadine and 5 mg of montelukast were administered. On the first day, peanut powder, at half the threshold dose of DBPCFC, was administered twice daily at 5-h and 30-min intervals. The OIT protocol consisted of 16 steps, corresponding to between 16 and 795 mg of peanut protein. Doses were increased from 9 to 55% with respect to measurement and feasibility (online suppl. Table 2S). Participants ingested peanut powder twice a day during their 5–12 days in hospital. If symptoms did not appear or only mild symptoms developed, the next dose was administered the following day, and if moderate or severe symptoms appeared, the same amount was administered the next day. After discharge from hospital, participants gradually increased the amount of pea-

nut powder ingested every 5 days up to 795 mg/day (target dose) at home. If mild adverse reactions appeared the dose was maintained, and if moderate or severe symptoms appeared the dose was reduced. If the dose was tolerated it was increased again. For the treatment of adverse reactions, we prescribed 10 mg of epinephrine, 1 mg/kg of prednisolone, epinephrine auto-injector (0.15 or 0.3 mg), and salbutamol sulfate to all children; we instructed the children and their guardians to use or administer the drugs, respectively, as needed. We also prepared a direct telephone line that was available at all times. Participants took maintenance doses daily, and the presence or absence of symptoms was recorded by their guardians daily. Participants visited our hospital every 1 to 3 months. When they were able to consume 795 mg of peanut protein without symptoms for 1 month, the premedication was withdrawn. Desensitization was defined as being able to consume 795 mg without symptoms after stopping premedication. When no symptoms were seen for 3 months, they underwent a second OFC after 2 weeks of complete peanut elimination to confirm sustained unresponsiveness.

Study Procedures

Immunological Parameters

We used peanut- and Ara h 2-specific IgE and IgG4 levels (ImmunoCAP assay system, Thermo Fisher Scientific, Uppsala, Sweden), measured at 0, 1, 3, 6, 12, 18, and 24 months for the OIT group and at the first and second OFCs for the historical control group.

Endpoints

The primary end point was the comparison of the second OFC between the OIT and historical control groups. The secondary endpoint was changes in peanut-specific IgE in both groups. We also evaluated changes in Ara h 2-specific IgE and peanut- and Ara h 2-specific IgG4 in the OIT group.

Table 1. Participant characteristics

	OIT group (n = 22)	Historical control group (n = 11)	p value
Age, years	8.5 (6.0–18.3)	7.9 (5.0–10.5)	ns ^b
Male	18 (81.8)	9 (81.8)	ns ^a
History of anaphylaxis due to peanut	22 (100)	11 (100)	ns ^a
<i>Complications</i>			
Bronchial asthma	11 (50.0)	5 (45.5)	ns ^a
Atopic dermatitis	13 (59.0)	6 (54.5)	ns ^a
Allergic rhinitis	12 (54.5)	6 (54.5)	ns ^a
Oral allergy syndrome	8 (36.3)	2 (18.1)	ns ^a
<i>Specific IgE, kUA/L</i>			
Peanut	38.5 (9.9–136)	15.7 (5.9–36.9)	<0.05 ^b
Ara h 2	36.6 (7.9–152)		
<i>Skin prick test</i>			
Wheal/erythema, mm	9 (6–10)/17(10–22)	10 (5–20)/20(10–38)	ns ^b
OFC (baseline)			
<i>Severity of symptoms</i>			
Mild	0 (0)	0 (0)	ns ^b
Moderate	17 (77.3)	9 (81.8)	
Severe	5 (22.7)	2 (18.2)	
<i>Threshold</i>			
Initial symptom, mg	33 (33–99)	99 (74–447)	<0.05 ^b
Anaphylaxis, mg	232 (136–431)	345 (321–570)	<0.05 ^b

Data are presented as *n* (%) or the median (interquartile range). OIT, oral immunotherapy; OFC, oral food challenge; ns, not significant. ^a Fisher exact test. ^b Wilcoxon rank sum test.

Statistical Analysis

The results of the statistical analysis are expressed as medians and ranges. Differences between groups for continuous variables were assessed using Wilcoxon rank-sum tests. Differences between groups for categorical data were examined using the Fisher exact test. A *p* value <0.05 was considered statistically significant. All analyses were performed with SPSS 24.0 software (IBM Corp., Armonk, NY, USA).

Ethics

The current study was conducted in accordance with the principles of the Declaration of Helsinki. Ethics approval was obtained through the Sagami-hara National Hospital Ethics Committee. Informed consent/assent was obtained for all patients and their parents. All data was anonymized prior to analysis.

Results

Participant Background

Twenty-nine participants with peanut allergy underwent DBPCFC; 25 exhibited anaphylactic reactions and 9 participants received intramuscular adrenaline. Of the

other patients, 8 developed respiratory symptoms and skin or gastrointestinal symptoms; moreover, following the administration of β_2 -inhalation, an antihistamine, and a steroid, their symptoms immediately improved. Eight patients developed gastrointestinal symptoms and skin symptoms, and, following the administration of an antihistamine and a steroid, their symptoms also improved. Three did not consent to participate in the OIT. Twenty-two participants underwent peanut OIT (Fig. 1). All participants displayed anaphylactic symptoms during the OFC (DBPCFC in the OIT group). The OIT group had 22 participants (median age 8.5 years), and the historical control group (median age 7.9 years) had 11. In the OIT group, 12 (54.5%) participants had a history of severe anaphylaxis to peanut (median number of incidents 2 times). The median peanut-specific IgE was 38.5 (9.9–136) kUA/L and Ara h 2-specific IgE was 36.6 (7.9–152) kUA/L. Prior to OIT, the median threshold to induce initial symptoms was 33 mg of peanut protein, and that to induce anaphylaxis was 232 mg of peanut protein. Compared to the historical control group, the number of anaphylactic episodes and the pea-

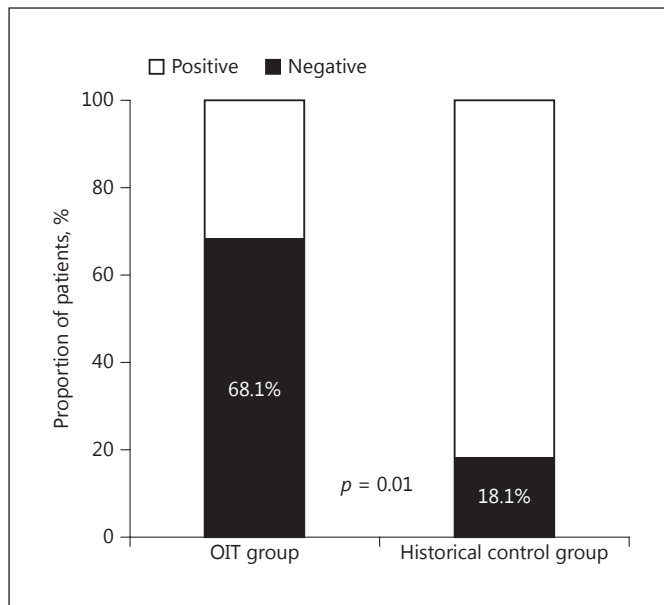


Fig. 3. Comparison of second OFC between the OIT and control groups at 2 years. Fisher exact test.

nut- and Ara h 2-specific IgE were significantly higher, and the threshold to induce initial symptoms and anaphylaxis were significantly lower in the OIT group (Table 1).

Clinical Outcomes

At the end of the rush phase, 5 participants (22.7%) were able to ingest 795 mg of peanut protein. All participants reached desensitization by 8 months (median 3 months) after the rush phase and those in the OIT group completed the protocol within 2 years. After 2 years, 15 participants (68.1%) in the OIT group achieved sustained unresponsiveness. On the other hand, only 2 participants (18.1%) in the historical control group passed the second OFC (Fig. 3).

Adverse Reactions and Treatment

During the rush phase, the percentage of doses per participant with any symptoms was 45.4%. Mucosal symptoms were most common, followed by those of the gastrointestinal tract and skin. Moderate symptoms comprised 7.2% of all symptoms, and severe symptoms comprised 1.0%. Three participants (13.6%) received intramuscular adrenaline during rush OIT because 2 developed persistent cough and 1 developed moderate abdominal pain.

During the home dosing phase, 5.6% of the total doses resulted in symptoms. Moderate symptoms comprised

Table 2. Adverse reactions and treatments

	Rush phase (n = 22)	Home dosing phase (n = 22)
Total number of times of peanut intake	207	7,611
<i>Adverse reaction</i>		
Any adverse reaction	94 (45.4)	433 (5.6)
Mild	77 (37.2)	391 (5.1)
Moderate	15 (7.2)	40 (0.5)
Severe	2 (1.0)	2 (0.02)
Skin	31 (14.9)	115 (1.5)
Mucosal	68 (32.8)	117 (1.5)
Gastrointestinal tract	40 (19.3)	127 (1.6)
Respiratory	14 (6.8)	165 (2.1)
Cardiovascular	0 (0)	1 (0.01)
Neurologic	2 (1.0)	9 (0.1)
<i>Treatment</i>		
Any treatment	24 (11.6)	89 (1.1)
Antihistamine	21 (10.1)	72 (0.9)
Steroid	3 (1.4)	21 (0.2)
β_2 -Inhalation	4 (1.9)	17 (0.2)
Adrenaline	3 (1.4)	2 (0.02)

Data are presented as n (%).

0.5%, and severe symptoms comprised 0.02%. Two participants (9.1%) received intramuscular adrenaline at home because 1 participant developed persistent cough and 1 developed moderate abdominal pain (Table 2).

Laboratory Data

The blood test results of 2 participants in the OIT group were missing; hence, 20 participants were evaluated. After 2 years, the median peanut-specific IgE levels in the OIT group had significantly decreased from 38.5 to 12.4 kUA/L, while there was no significant change in the historical control group (Fig. 4).

Median peanut-specific IgE levels in the OIT group significantly increased to 53.5 kUA/L at 1 month after rush OIT and decreased significantly to 33.9 kUA/L at 6 months, 18.2 kUA/L at 1 year, and 12.8 kUA/L at 2 years. Ara h 2-specific IgE levels increased significantly to 47.8 kUA/L at 1 month and gradually decreased to 29.7 kUA/L at 6 months, 16.1 kUA/L at 1 year, and 7.5 kUA/L at 2 years (online suppl. Fig. S1).

Median peanut-specific IgG4 levels in the OIT group increased significantly from baseline after 1 month. Similarly, Ara h 2-specific IgG4 also increased significantly after 1 month (online suppl. Fig. S2).

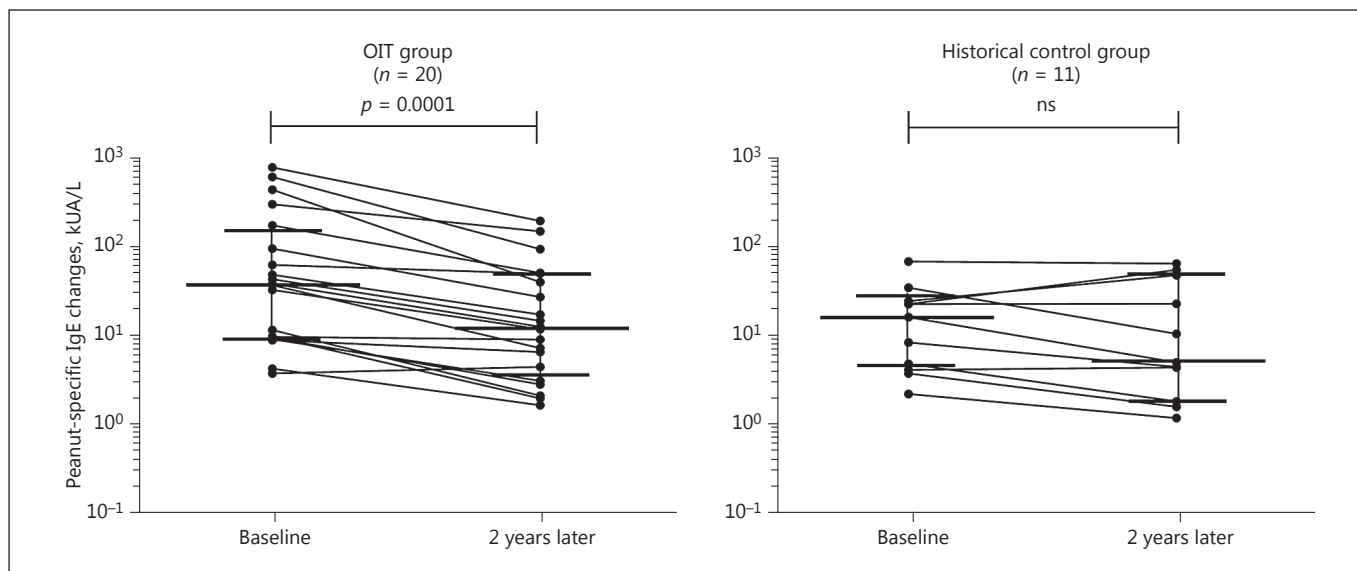


Fig. 4. Comparison of changes in peanut-specific IgE levels. Wilcoxon rank-sum test.

Discussion

This is the first report on peanut OIT for patients with confirmed anaphylactic symptoms. After 2 years, unresponsiveness, confirmed with a second OFC, increased significantly in the OIT group (68.1%) compared to the historical control group (18.1%), whereas peanut-specific IgE decreased significantly (Fig. 3, 4).

Previous reports have evaluated sustained unresponsiveness with peanut OIT [14, 15, 22]. For example, Blumchen et al. [22] reported that their peanut OIT consisted of an initial rush phase (7 days), a long-term build-up phase (0–20 months), and a maintenance phase (2 months) for peanut-allergic children (median age 5.6 years). Over 80% of participants had a history of allergic reactions according to accidental peanut ingestion, and the median peanut-specific IgE level was 95.6 kUA/L. In this study, 4 participants (18%) achieved sustained unresponsiveness to 500 mg of peanut protein after 2 weeks of peanut avoidance, thus their outcome was lower than that in our study. This may be because of the differences in duration of the maintenance phase between the 2 studies. Moreover, it has been suggested that achieving sustained unresponsiveness might be enhanced with longer treatment durations [23]. In the study by Blumchen et al. [22] the maintenance phase was only 2 months, which was shorter than that of our study. Furthermore, the maintenance dose was 125 mg of peanut protein, which was less than that in our study. In addition, Brian et al. [15] re-

ported that peanut OIT consisted of an initial escalation day, a build-up phase, and a home-dosing phase. They excluded patients who had a history of severe, life-threatening anaphylaxis. The mean length of treatment was 1,453 days up to 5 years. In that study, 50% of 24 participants successfully passed a challenge 1 month after stopping OIT; this is also lower than that in our study and may be because the target dose of OFC was higher (5 g of peanut protein) and the avoidance period before the OFC was longer (1 month). In our study, all patients had a history of anaphylaxis and demonstrated anaphylactic symptoms at DBPCFC. These data suggest that our study included more severe allergic patients than did previous studies. The treatment outcome also indicates great effectiveness, with 68.1% of participants achieving unresponsiveness to 795 mg of peanut protein.

Previous reports have examined adverse reactions during OIT for peanut allergy. For instance, Blumchen et al. [22] reported a lower percentage of adverse events per doses, compared to that in our report. This may be because the minimum ingestion dose for the maintenance phase of this prior study was lower, with 125 mg of peanut protein as the target dose. Adverse reactions to slow OIT have been reported, including itching in the oral cavity (6.3%), the frequency of β_2 -inhalation (0.35%), and adrenaline administration (0.01%; twice) [12]. This is similar to the results of our study regarding adverse reactions that patients experienced with home doses. In contrast, Hofmann et al. [24] reported that adrenaline was adminis-

tered to 4 participants (14%) on the initial escalation days. In our study, the percentage of reactions requiring any treatment was 1.7% at home during the buildup phase and 0.7% during the maintenance phase, with 2 participants receiving adrenaline. Accordingly, there appear to be no major differences among studies regarding safety.

Moreover, peanut- and Ara h 2-specific IgG4 increased significantly from baseline after 1 month (online suppl. Fig. S2). Jones et al. [25] reported that peanut-specific IgG4 increased after 3 months of treatment, whereas increased levels were observed after 1 month in the report by Nozawa et al. [13] and our study. This discrepancy is probably due to the rush phase that existed both in our study and the report by Nozawa et al. [13].

These results demonstrate that the safety was similar to that of the previous study and that a high treatment outcome was achieved, even when OIT was performed for patients with a highly severe condition.

A limitation of this study is that 2 weeks of avoidance to assess sustained unresponsiveness might have been insufficient [11]. However, our participants underwent OIT to prevent anaphylactic symptoms according to accidental exposure. Thus, if patients were able to ingest peanut after 2 weeks of avoidance, the risk of anaphylaxis is decreased in daily life. Furthermore, some reports assessed sustained unresponsiveness using 2 weeks of avoidance [19, 26].

There were differences in patient characteristics between the OIT group and the historical control groups. However, in terms of peanut-specific IgE thresholds to

induce initial symptoms and anaphylactic symptoms, the severity seemed to be higher in the OIT group. Nevertheless, the treatment outcome was better in the OIT group, and the peanut-specific IgE decreased significantly, suggesting that these characteristic differences had minimal, if any, effects on the results. The reason for the difference of severity may be that a history of more anaphylactic events caused these participants and their parents to strongly desire OIT. The reason for anaphylaxis appearance in DBPCFC might be that the initial dose was 33 mg of peanut protein. We chose this amount as the initial dose because it was difficult to accurately measure amounts below 33 mg when mixed with strawberry puree. Another limitation is that Ara h 2-specific IgE was not measured in the historical control group because conventional measurement of Ara h 2-specific IgE was not available in Japan at that time.

In conclusion, for patients with severe anaphylaxis to peanuts, OIT increased the threshold and helped achieve sustained unresponsiveness. Further studies are needed to investigate efficacy for tolerance induction by OIT for anaphylactic patients.

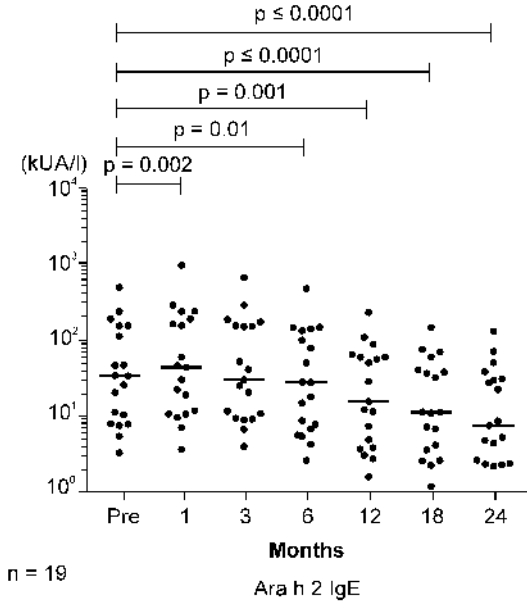
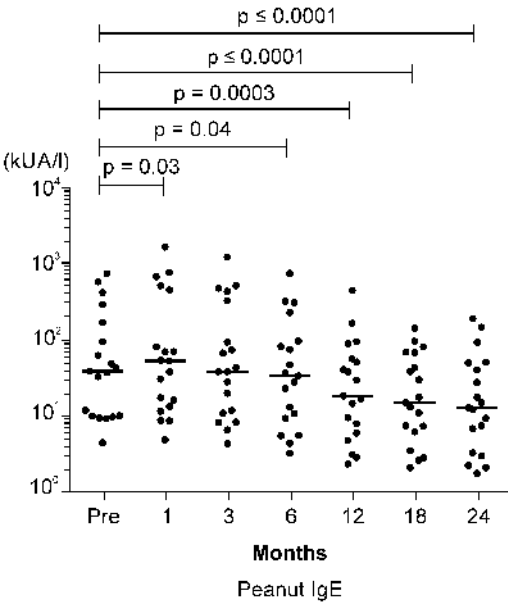
Disclosure Statement

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

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 Worm M, Moneret-Vautrin A, Scherer K, Lang R, Fernandez-Rivas M, Cardona V, Kowalski ML, Jutel M, Poziomkowska-Gesicka I, Papadopoulos NG, Beyer K: First European data from the network of severe allergic reactions (NORA). *Allergy* 2014;69:1397–1404.
- 4 Bock SA, Munoz-Furlong A, Sampson HA: Further fatalities caused by anaphylactic reactions to food, 2001–2006. *J Allergy Clin Immunol* 2007;119:1016–1018.
- 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, Asai Y, Chan E, Cheuk S, Shand G, St-Pierre Y, Harada L, Allen M, Clarke A: Accidental exposures to peanut in a large cohort of Canadian children with peanut allergy. *Clin Transl Allergy* 2015;5:16.
- 8 Muraro A, Werfel T, Hoffmann-Sommergruber K, Roberts G, Beyer K, Bindslev-Jensen C, Cardona V, Dubois A, Dutoit G, Eigenmann P, Fernandez Rivas M: EAACI food allergy and anaphylaxis guidelines: diagnosis and management of food allergy. *Allergy* 2014;69:1008–1025.
- 9 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.
- 10 Peters RL, Allen KJ, Dharmage SC, Koplin JJ, Dang T, Tilbrook KP, Lowe A, Tang ML, Gurrin LC: 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.
- 11 Wood RA: Food allergen immunotherapy: current status and prospects for the future. *J Allergy Clin Immunol* 2016;137:973–982.

- 12 Anagnostou K, Islam S, King Y, Foley L, Pasea L, Bond S, Palmer C, Deighton J, Ewan P, Clark A: 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 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.
- 14 Tang ML, Ponsonby AL, Orsini F, Tey D, Robinson M, Su EL, Licciardi P, Burks W, Donath S: Administration of a probiotic with peanut oral immunotherapy: a randomized trial. *J Allergy Clin Immunol* 2015;135:737–744.
- 15 Vickery BP, Scurlock AM, Kulis M, Steele PH, Kamilaris J, Berglund JP, Burk C, Hiegel A, Carlisle S, Christie L, Perry TT: Sustained unresponsiveness to peanut in subjects who have completed peanut oral immunotherapy. *J Allergy Clin Immunol* 2014;133:468–475.
- 16 Simons FE: Anaphylaxis. *J Allergy Clin Immunol* 2010;125:S161–S181.
- 17 Simons FE, Arduoso LR, Bilò MB, El-Gamal YM, Ledford DK, Ring J, Sanchez-Borges M, Senna GE, Sheikh A, Thong BY; World Allergy Organization: World allergy organization guidelines for the assessment and management of anaphylaxis. *World Allergy Organ J* 2011;4:13–37.
- 18 Ebisawa M, Nishima S, Ohnishi H, Kondo N: Pediatric allergy and immunology in Japan. *Pediatr Allergy Immunol* 2013;24:704–714.
- 19 Sato S, Utsunomiya T, Imai T, Yanagida N, Asaumi T, Ogura K, Koike Y, Hayashi N, Okada Y, Shukuya A, Ebisawa M: Wheat oral immunotherapy for wheat-induced anaphylaxis. *J Allergy Clin Immunol* 2015;136:1131–1133.
- 20 Ebisawa M, Ito K, Fujisawa T; Committee for Japanese Pediatric Guideline for Food Allergy, The Japanese Society of Pediatric Allergy and Clinical Immunology, The Japanese Society of Allergology: Japanese guidelines for food allergy 2017. *Allergol Int* 2017;66:248–264.
- 21 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;173:173–182.
- 22 Blumchen K, Ulbricht H, Staden U, Dobberstein K, Beschornier J, de Oliveira LC, Shreffler WG, Sampson HA, Niggemann B, Wahn U, Beyer K: Oral peanut immunotherapy in children with peanut anaphylaxis. *J Allergy Clin Immunol* 2010;126:83–91.
- 23 Jones SM, Burks AW, Keet C, Vickery BP, Scurlock AM, Wood RA, Liu AH, Sicherer SH, Henning AK, Lindblad RW, Dawson P, Berin C, Fleischer DM, Leung DY, Plaut M, Sampson HA: Long-term treatment with egg oral immunotherapy enhances sustained unresponsiveness that persists after cessation of therapy. *J Allergy Clin Immunol* 2016;137:1117–1127.
- 24 Hofmann AM, Scurlock AM, Jones SM, Palmer KP, Lokhnygina Y, Steele PH, Kamilaris J, Burks AW: Safety of a peanut oral immunotherapy protocol in children with peanut allergy. *J Allergy Clin Immunol* 2009;124:286–291.
- 25 Jones S, Pons L, Roberts J, Scurlock AM, Perry TT, Kulis M, Shreffler WG, Steele P, Henry KA, Adair M, Francis JM: Clinical efficacy and immune regulation with peanut oral immunotherapy. *J Allergy Clin Immunol* 2009;124:292–300.
- 26 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.

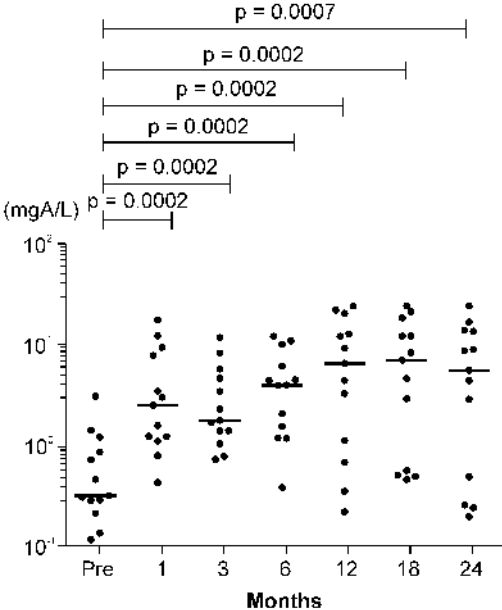


Wilcoxon's rank sum test

Supplementary Figure Legends

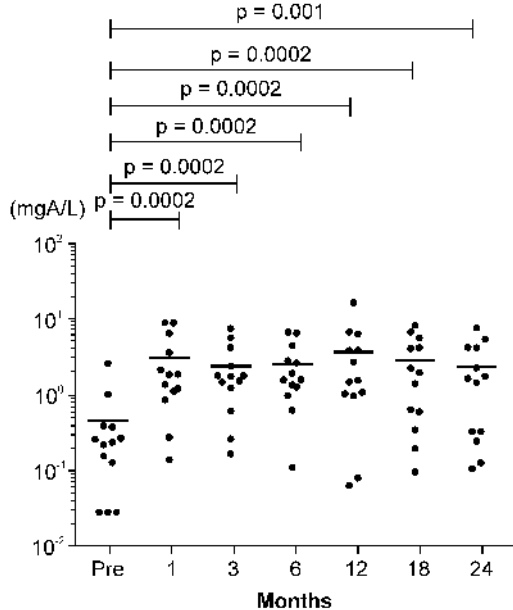
Fig. S1. Changes in specific IgE in the OIT group.

Fig. S2. Changes in specific IgG4 in the OIT group.



Peanut IgG4

$n = 13$



Ara h 2 IgG4

Wilcoxon's rank sum test

Table S1. Severity grading of adverse reactions

	Mild	Moderate	Severe
Skin	Localized urticaria, wheal, pruritus, weak itching	Generalized urticaria, wheal, pruritus, strong itching	
Mucosal tissue	Swollen eyelid or lip, pruritus of the throat or oral cavity	Swollen whole face, throat pain	Tightness of throat, difficulty swallowing, hoarseness
Gastrointestinal tract	Mild abdominal pain, nausea, emesis, diarrhea	Moderate abdominal pain, recurrent emesis, diarrhea	Continuous emesis, loss of bowel control
Respiratory tract	Intermittent cough, nasal congestion, sneezing, rhinorrhea	Repetitive cough, chest tightness, mild wheezing	Persistent cough, hoarseness, "barky" cough, apparent wheezing, dyspnea, cyanosis, saturation <92%, respiratory arrest
Cardiovascular		Facial pallor, mild hypotension, tachycardia (increase >15 beats/min)	Hypotension, dysrhythmia, severe bradycardia, cardiac arrest
Neurological	Change in activity level, tiredness	Feeling of "pending doom", somnolence, lightheadedness	Confusion, loss of consciousness, incontinence

Hypotension was defined as systolic blood pressure: 1 month to 1 year <70 mmHg, 1–10 years <[70 mmHg + (2 × age)]: 11–17 years <90 mmHg. Mild hypotension was defined as systolic blood pressure: 1 month to 1 year <80 mmHg, 1–10 years <[80 mmHg + (2 × age)]: 11–17 years <100 mmHg.

Table S2. Dosing schedule of OIT

Step	Peanut protein (mg)	Whole peanut (mg)	Rate of increase from the previous step
1	16	60	
2	24	90	50%
3	37	140	55%
4	53	200	43%
5	80	300	50%
6	119	450	50%
7	186	700	55%
8	265	1,000	42%
9	331	1,250	25%
10	398	1,500	20%
11	464	1,750	17%
12	530	2,000	14%
13	596	2,250	13%
14	663	2,500	11%
15	729	2,750	10%
16	795	3,000	9%

Doses were increased from 9% to 55% because of measurement and feasibility.