

ORIGINAL ARTICLE

Low-dose-oral immunotherapy for children with wheat-induced anaphylaxis

Ken-ichi Nagakura^{1,2}  | Noriyuki Yanagida¹ | Sakura Sato^{3,4} | Makoto Nishino^{1,4} | Kyohei Takahashi^{1,4}  | Tomoyuki Asaumi¹  | Kiyotake Ogura^{1,4} | Motohiro Ebisawa^{2,3} 

¹Department of Pediatrics, National Hospital Organization Sagami National Hospital, Kanagawa, Japan

²Department of Pediatrics, Jikei University School of Medicine, Tokyo, Japan

³Department of Allergy, Clinical Research Center for Allergy and Rheumatology, National Hospital Organization Sagami National Hospital, Kanagawa, Japan

⁴Course of Allergy and Clinical Immunology, Juntendo University Graduate School of Medicine, Tokyo, Japan

Correspondence

Motohiro Ebisawa, Department of Allergy, Clinical Research Center for Allergy and Rheumatology, National Hospital Organization, Sagami National Hospital, 18-1, Sakurada, Minami-ku, Sagami, Kanagawa 252-0392, Japan.
Email: mebisawa@foodallergy.jp

Funding information

This work was supported by the Health and Labour Sciences Research Grants for Research on Allergic Disease and Immunology from the Ministry of Health, Labour and Welfare of Japan [Motohiro Ebisawa, Grant number: 201414009A] and the Practical Research Project for Allergic Disease and Immunology from the Japan Agency for Medical Research and Development [AMED, 17ek0410019h0003].

Editor: Hugh Sampson

Abstract

Background: Oral immunotherapy (OIT) use in patients with wheat anaphylaxis is not well studied. We assessed the efficacy of low-dose OIT for patients with wheat-induced anaphylaxis.

Methods: Eligible subjects were aged 5-18 years with a history of wheat anaphylaxis and confirmed symptoms during oral food challenge (OFC) to 53 mg of wheat protein. After admission to the hospital for a 5-day buildup phase, patients in the OIT group gradually increased wheat ingestion to 53 mg/day and then ingested 53 mg daily at home. One year later, they underwent 53- and 400-mg OFCs after OIT cessation for 2 weeks. The historical control group was defined as patients who avoided wheat during the same period.

Results: Median wheat- and ω -5 gliadin-specific immunoglobulin E (IgE) levels were 293 and 7.5 kU_A/L, respectively, in the OIT group (16 children). No patients dropped out. Within 1 year, 88% of patients in the OIT group reached 53 mg. After 1 year, 69% and 9% patients passed the 53-mg OFC and 25% and 0% passed the 400-mg OFC in the OIT and control groups (11 children), respectively ($P = .002$ and 0.07 , respectively). In the OIT group, wheat- and ω -5 gliadin-IgE levels significantly decreased to 154 and 4.1 kU_A/L, respectively, at 1 year, and wheat- and ω -5 gliadin-specific IgG and IgG₄ levels significantly increased at 1 month. Anaphylaxis developed 7 times and promptly improved without adrenaline.

Conclusion: For patients with wheat anaphylaxis, low-dose OIT safely induces immunologic changes, achieves low-dose desensitization, and may allow for a 400 mg dose.

KEYWORDS

anaphylaxis, desensitization, food allergy, immunoglobulin E, oral immunotherapy, oral food challenge, severe, wheat, ω -5 gliadin, OFC, OIT

1 | INTRODUCTION

Wheat is a major cause of food allergy^{1,2} accounting for 17.7% of anaphylactic food reactions in Japan.³ While most infants with wheat allergy acquire tolerance, school-aged children are unlikely to do so.^{4,5} Furthermore, patients with severe wheat allergy, such as those with high wheat-specific immunoglobulin E (sIgE) levels and a history of anaphylaxis, have difficulty in acquiring tolerance.^{4,5} Even if wheat allergy patients ingest low doses of wheat, anaphylaxis may develop.⁶

Although the efficacy of oral immunotherapy (OIT) has been reported, severe adverse reactions often occur.⁷⁻¹⁰ Particularly, high levels of antigen sIgE pose a risk for severe adverse reactions during wheat OIT.¹¹⁻¹⁵ Therefore, safer methods of wheat OIT are necessary.

The efficacy of low-dose OIT for patients with hen's egg, cow's milk, and peanut allergy has been recently reported.¹⁶⁻²⁰ Moreover, low-dose OIT is safer than conventional OIT, enabling patients to ingest low doses in their diet without developing symptoms.^{9,21} Furthermore, low-dose OIT may be effective in preventing symptoms caused by accidental ingestion.^{20,22} Herein, we assessed low-dose OIT efficacy and safety for children with severe wheat allergy with the aim of preventing symptoms from accidental exposure by contamination.

2 | Methods

2.1 | Study design

This was a prospective nonrandomized trial conducted at Sagami National Hospital between 2013 and 2015. The participants were children aged 5-18 years with a history of wheat anaphylaxis. Anaphylaxis was defined according to the World Allergy Organization guidelines.^{23,24} The criterion for eligibility was development of objective reactions during an oral food challenge (OFC) to 53 mg of wheat protein.

Because many facilities perform OIT in Japan and our facility is an allergic care core hospital,²⁵ patients visited our hospital to receive OIT; thus, it was difficult to conduct a randomized controlled trial (RCT). Therefore, we designed a historical control group consisting of children aged 5 years or over with a history of anaphylaxis who developed reactions upon 53-mg OFC between 2013 and 2015 and who strictly avoided wheat up to the second OFC for 1 year. All patients underwent a 53-mg OFC 1 year later. If they passed the 53-mg OFC, they underwent a 400-mg OFC (Figure 1).

2.2 | OFC

We used approximately 2 g of boiled *udon* noodle, containing 53 mg of wheat protein, for the baseline OFC, and 15 g of boiled *udon* noodle, containing 400 mg of wheat protein (equivalent to a piece of cookie/biscuit), for the final OFC for both groups.

Key Message

Low-dose oral immunotherapy (OIT) may be considered as suitable management for severe wheat allergy presenting with anaphylaxis.

A quarter of OFC food was provided initially, and the remaining three-quarters were provided 60 minutes later. Positive OFC was defined as objective symptom appearance, at which point the intake was discontinued. We assessed the severity of symptoms as mild, moderate, or severe based on the Japanese guidelines for food allergy (Table S1).²⁶ If the baseline OFC was positive, OIT was started the next day.

2.3 | OIT protocol

Patients were admitted to the hospital for 5 days. Premedication with 10 mg of loratadine was administered, and then, patients consumed the wheat at half the threshold of the baseline OFC (Figure 2). Our OIT protocol entailed an 8-step increase in the dose starting from 2.7 to 53 mg. If there were no or mild symptoms, the amount for the next day was increased by 1 step (Table S2). At the beginning of OIT, we instructed guardians on symptom management and that adrenaline auto-injector should be promptly used in case of anaphylaxis.^{23,24} We asked them to keep a daily record of ingestion detail and severity of symptoms. Furthermore, we offered direct telephone support for OIT patients 24 hours a day, 365 days a year. After discharge, the same dose as that ingested on the fifth day was to be continued every day for 1 month. After that, if the patients were able to ingest wheat while asymptomatic for 5 consecutive days, as with other previously described antigen low-dose OIT protocols,¹⁷⁻¹⁹ the dose was increased at the patients' home by 1 step up to 53 mg per day. If moderate or severe symptoms appeared, the dose was decreased by one or two steps, respectively. If patients were able to ingest 53 mg for 1 month without being symptomatic, premedication was terminated. One year after initiation of OIT, patients underwent 53- and 400-mg OFCs on 2 consecutive days after the cessation of OIT for 2 weeks. If patients had passed these OFCs, they were allowed to ingest 15 g of *udon* noodle or a piece of cookie/biscuit in their daily diet.

2.4 | Definition

"Low-dose desensitization" was defined as when patient could ingest 53 mg without symptoms. Meanwhile, "short-term unresponsiveness to 400 mg" was defined as passing the 400-mg OFC after 2 weeks of complete elimination. Japanese food allergy guideline defines 50-75 mg as a "low dose," equal to the lowest level of contamination, and 400-1300-mg as a "medium dose."²⁶ If patients were able to ingest 400 mg, they were allowed to intake 15 g of *udon* noodle

FIGURE 1 Patient inclusion flowchart. OFC: oral food challenge; OIT: oral immunotherapy

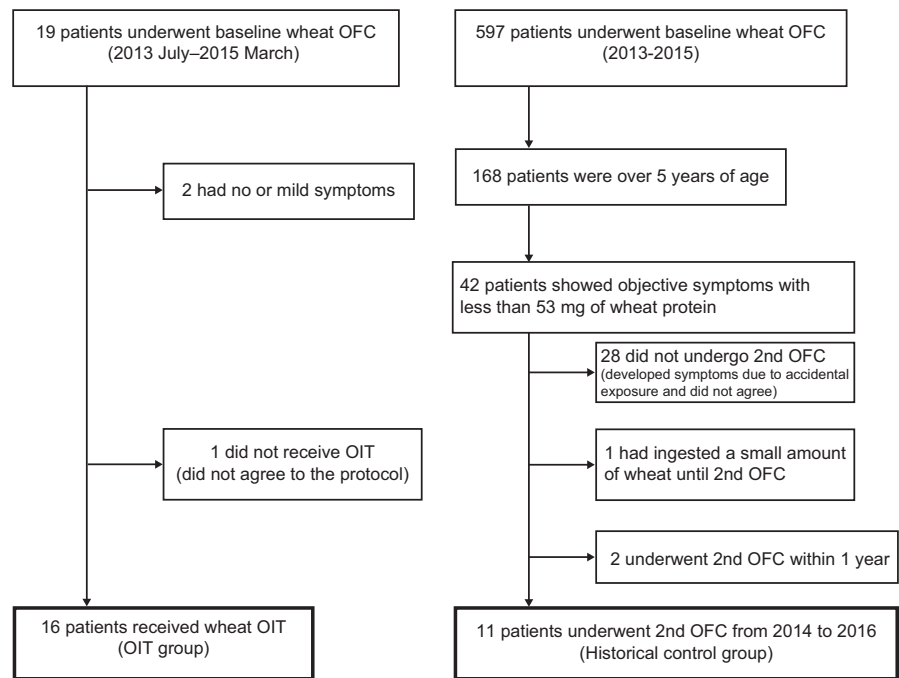
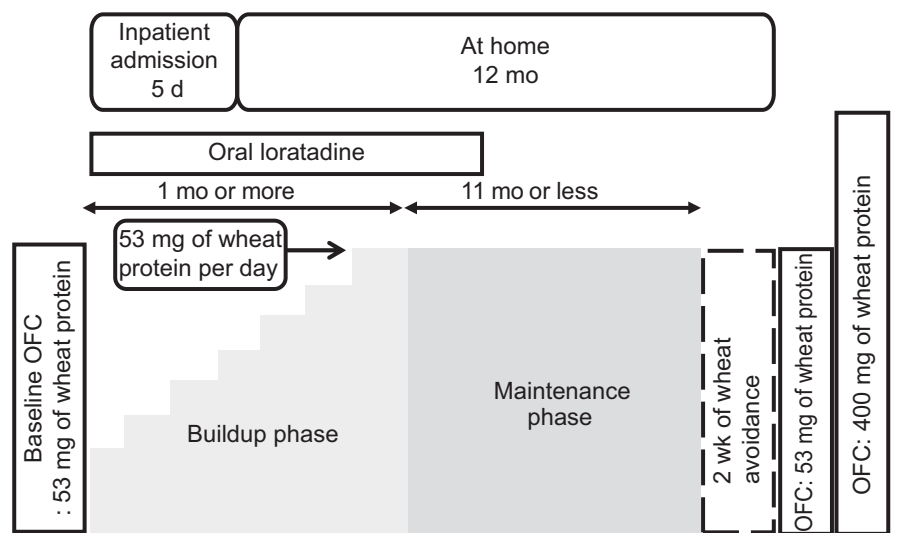


FIGURE 2 OIT protocol. OIT: oral immunotherapy; OFC: oral food challenge



or a piece of cookie/biscuit in their daily diet. Therefore, the risk of symptom from accidental exposure would decrease if patients could consume 400 mg. In addition, the risk of resuming intake after an unexpected discontinuation due to viral infections would decrease if patients were able to consume wheat after 2 weeks of avoidance.²⁷

2.5 | Immunologic parameters

sIgE, specific IgG (sIgG), and specific IgG₄ (sIgG₄) to wheat and ω -5 gliadin were measured using ImmunoCAP assay system (Thermo Fisher Scientific/Phadia AB) at baseline and after 1, 3, 6, and 12 months in the OIT group and at baseline and 12 months in the historical control group.

2.6 | End-points

The primary end-point was short-term unresponsiveness to 400 mg after 1 year. The secondary end-points were passing the 53-mg OFC after 2 weeks of avoidance, changes in laboratory data, and adverse reactions within 1 year.

2.7 | Statistical analysis

The derived values are summarized as the median and range. Differences in categorical data were analyzed using Fisher's exact test, while differences in continuous variables between the 2 groups were tested using Wilcoxon rank-sum tests. A *P*-value < .05 was

considered significant. All data were processed and summarized using SPSS 24.0 software (IBM Corp.).

2.8 | Ethical considerations

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Sagamiara National Hospital Ethics Committee (Approval No.: 2013070916). The study design and risk of symptoms were explained to all patients and their guardians, and written informed consent and assent were obtained. All data were anonymized prior to analysis.

3 | RESULTS

3.1 | Study population

Nineteen patients with wheat anaphylaxis underwent the 53-mg OFC. Two had no symptoms during OFC. One did not agree to the OIT protocol. Therefore, 16 patients received the low-dose wheat OIT. The historical control group consisted of 11 patients (Figure 1). In the OIT group, the median threshold of baseline OFC was 39.8 mg, and the median wheat- and ω -5 gliadin-sIgE levels were 293 kU_A/L and 7.5 kU_A/L, respectively. There were no significant differences between the 2 groups (Table 1).

3.2 | Clinical outcomes

None of the patients dropped out from the protocol. During the hospitalization at the beginning of OIT, 5 of the 16 patients (31%) had no symptoms. Within 1 year, 14 patients (88%) achieved low-dose desensitization (median, 2 months; range, 1-8 months). Two patients (13%) did not reach 53 mg because of adverse reactions (one due to skin symptoms and one due to mucosal and gastrointestinal symptoms) at home. Ingestion amount was 39.8 mg and 18.6 mg at 12 months, respectively. One year after start of OIT, 11 patients (69%) passed the 53-mg OFC, following 2 weeks of OIT cessation. Furthermore, 4 patients (25%) passed the 400-mg OFC the next day; therefore, they were defined as having a short-term unresponsiveness to 400 mg. By contrast, a single patient passed the 53-mg OFC, and no patient passed the 400-mg OFC in the historical control group. The proportion of patients passing the 53-mg OFC was significantly higher in the OIT group than in the historical control group ($P = .002$). Meanwhile, the number of participants achieving short-term unresponsiveness to 400 mg tended to be higher in the OIT group than in the historical control group ($P = .07$) (Figure 3).

3.3 | Adverse reactions

We analyzed adverse reactions for all patients from baseline to 12 months in both OIT and historical control groups (Table 2). We

	OIT group (n = 16)	Historical control group (n = 11)	P value
Age (years)	6.7 (5.8-10.7)	6.4 (5.0-8.1)	.33
Male, n (%)	12 (75.0%)	9 (81.8%)	.68
History of anaphylaxis to wheat, n (%)	16 (100.0%)	11 (100.0%)	-
Current complications, n (%)			
BA	9 (56.2%)	5 (45.5%)	.58
AD	10 (62.5%)	4 (36.4%)	.18
AR	5 (31.3%)	4 (36.4%)	.78
Severity of symptoms during OFC	Mild: 2; Moderate: 12; Severe: 2	Mild: 1; Moderate: 8; Severe: 2	>.999
Threshold of baseline OFC (mg)	39.8 (3.4-53)	53.0 (10.6-53)	.87
Specific IgE (kU _A /L)			
Wheat	293 (4.5-3340)	41.6 (8.2-2370)	.14
ω -5 gliadin	7.5 (0.1-469)	3.5 (0.15-59.6)	.30
Specific IgG (mgA/L)			
Wheat	19.8 (8.3-67.2)	23.4 (7.9-41.2)	.41
ω -5 gliadin	6.0 (2.2-23.4)	5.5 (4.4-22.6)	.82
Specific IgG ₄ (mgA/L)			
Wheat	2.07 (0.09-21.9)	2.84 (0.24-18.6)	.57
ω -5 gliadin	0.07 (0.03-1.1)	0.03 (0.03-0.79)	.89

TABLE 1 Characteristics of the patients in the OIT and historical control groups

Abbreviations: AD, atopic dermatitis; AR, allergic rhinitis; BA, bronchial asthma; OIT, oral immunotherapy; OFC, oral food challenge.

FIGURE 3 Comparison of clinical outcomes (53 mg or 400 mg of wheat protein). OFC: oral food challenge; OIT: oral immunotherapy

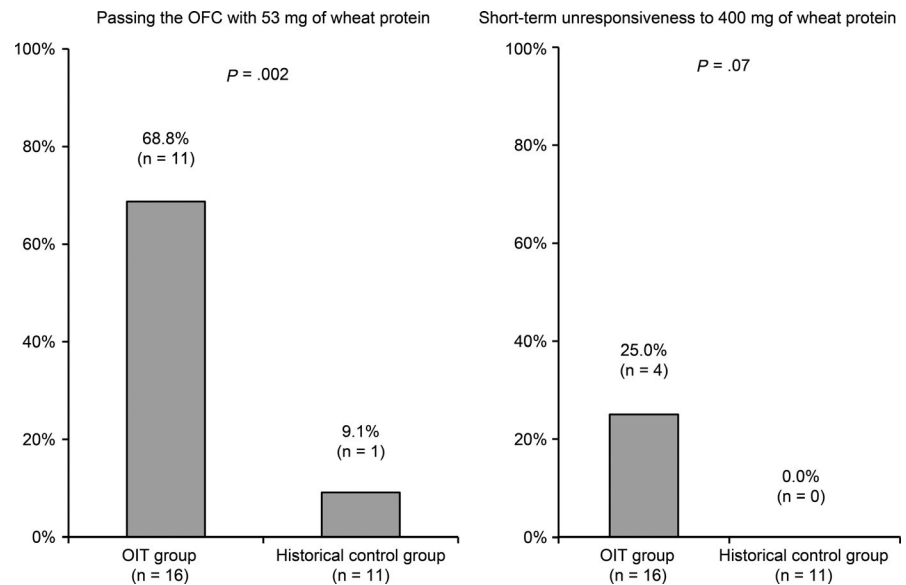


TABLE 2 Adverse reactions and corresponding treatments administered during the OIT protocol

Adverse reactions and treatments			Hospital		Home	
Total number of intakes of OIT			81		5857	
Total number of adverse reactions			26 (32.1%)		242 (4.1%)	
	Mild	Moderate	Severe	Mild	Moderate	Severe
Gastrointestinal symptoms	11 (13.6%)	0 (0.0%)	0 (0.0%)	78 (1.3%)	8 (0.1%)	0 (0.0%)
Oral mucosal symptoms	8 (9.9%)	0 (0.0%)	0 (0.0%)	59 (1.0%)	4 (0.07%)	0 (0.0%)
Skin symptoms	7 (8.6%)	5 (6.2%)	0 (0.0%)	47 (0.8%)	24 (0.4%)	0 (0.0%)
Respiratory symptoms	5 (6.2%)	6 (7.4%)	0 (0.0%)	73 (1.2%)	27 (0.5%)	0 (0.0%)
Cardiovascular symptoms	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Anaphylaxis	0 (0.0%)			7 (0.1%)		
Total number of reactions needing any treatments	15 (18.5%)			82 (1.4%)		
Antihistamine	13 (16.0%)			74 (1.3%)		
Steroid	1 (1.2%)			15 (0.3%)		
β_2 -inhalation	8 (9.9%)			43 (0.7%)		
Adrenaline	0 (0.0%)			0 (0.0%)		

OIT, oral immunotherapy.

We analyzed all patients' adverse reactions and treatment from the initiation of OIT to one year later.

No patient developed eosinophilic gastro-intestinal disorder included eosinophilic esophagitis, eosinophilic gastritis, eosinophilic gastroenteritis, eosinophilic enteritis, and eosinophilic colitis.

showed all adverse reactions stratified by severity for each organ system. In the OIT group, the rate of symptoms per ingestion during admission was 32.1%. Anaphylaxis was not observed during hospitalization. Meanwhile, the rate of symptoms for the home doses was 4.1%. Five patients developed anaphylaxis for a total of 7 events. There were 6 instances of a combination of moderate skin and respiratory symptoms which promptly improved with β_2 -stimulant inhalation, antihistamine,

and steroids. A combination of moderate skin and oral mucosal symptoms was promptly improved with antihistamine and steroids. Of 5 patients who developed anaphylaxis, one achieved short-term unresponsiveness and one did not reach low-dose desensitization. All 7 anaphylactic reactions developed not only on the day of the new dosing, but also when ingesting the same dose as the one on the previous day. Five anaphylaxis events occurred in the buildup phase, while two

occurred in the maintenance phase. During the OIT protocol, no severe symptoms developed. Furthermore, no patient had accidental wheat exposure in the historical control group.

3.4 | Laboratory data

Median 12-month wheat- and ω -5 gliadin-sIgE levels were significantly decreased compared to those at baseline in the OIT group (153.5 kU_A/L, 4.1 kU_A/L, respectively) ($P = .04$, $P = .009$). Meanwhile, median wheat- and ω -5 gliadin-sIgG levels increased significantly from baseline to 1 month (24.1 and 7.3 mgA/L, respectively) ($P = .004$, $P = .02$). Median wheat- and ω -5 gliadin-sIgG₄ levels increased significantly from baseline to 1 month (4.7 mgA/L, 0.09 mgA/L, respectively) ($P = .01$, $P = .009$) (Figure 4). By contrast, median wheat- and ω -5 gliadin-sIgE levels were unchanged in the historical control group. The 12-month median wheat-sIgG and wheat-sIgG₄ levels were significantly lower than those at baseline, while median ω -5 gliadin-sIgG and ω -5 gliadin-sIgG₄ levels were unchanged (Figure S1). At 12 months, wheat-sIgG₄ levels for the OIT group were significantly higher than those for the historical control group ($P = .01$); there was no significant difference in other laboratory data.

4 | DISCUSSION

We performed low-dose OIT for patients with severe wheat allergy. We found that low-dose OIT induces low-dose desensitization and immunologic changes without causing severe symptoms. Furthermore, low-dose OIT may yield short-term unresponsiveness to 400 mg in some patients.

For patients with severe food allergy, the ability to consume low doses of the causative food can reduce the risk of symptoms due to accidental ingestion, improving the quality of life.^{20,22} In the present study, 88% of patients reached low-dose desensitization and 69% passed the 53-mg OFC after 2 weeks of avoidance, and this rate was significantly higher than that in the historical control group (9%). These results are comparable to those achieved in previous reports using low-dose OIT with target dose of 102 mg of milk protein and 133 mg of peanut protein.^{17,19} Although there was no significant difference, the proportion of patients achieving short-term unresponsiveness to 400 mg was 25%, higher than that in the historical control group (0%). We previously conducted a rush OIT in which 61% of patients achieved short-term unresponsiveness to 5200 mg 2 years after starting OIT.¹² By contrast, the maintenance dose in the current study was 53 mg, and the study was conducted in 1 year. Because of the low target dose and short treatment period, the rate of achieving short-term unresponsiveness is low compared with previous rush OIT.

Although we completed the protocol of low-dose OIT without severe symptoms requiring intramuscular adrenaline, some trials of wheat OIT have reported the development of severe symptoms.^{12,13,15} In our previous report on rush OIT that described

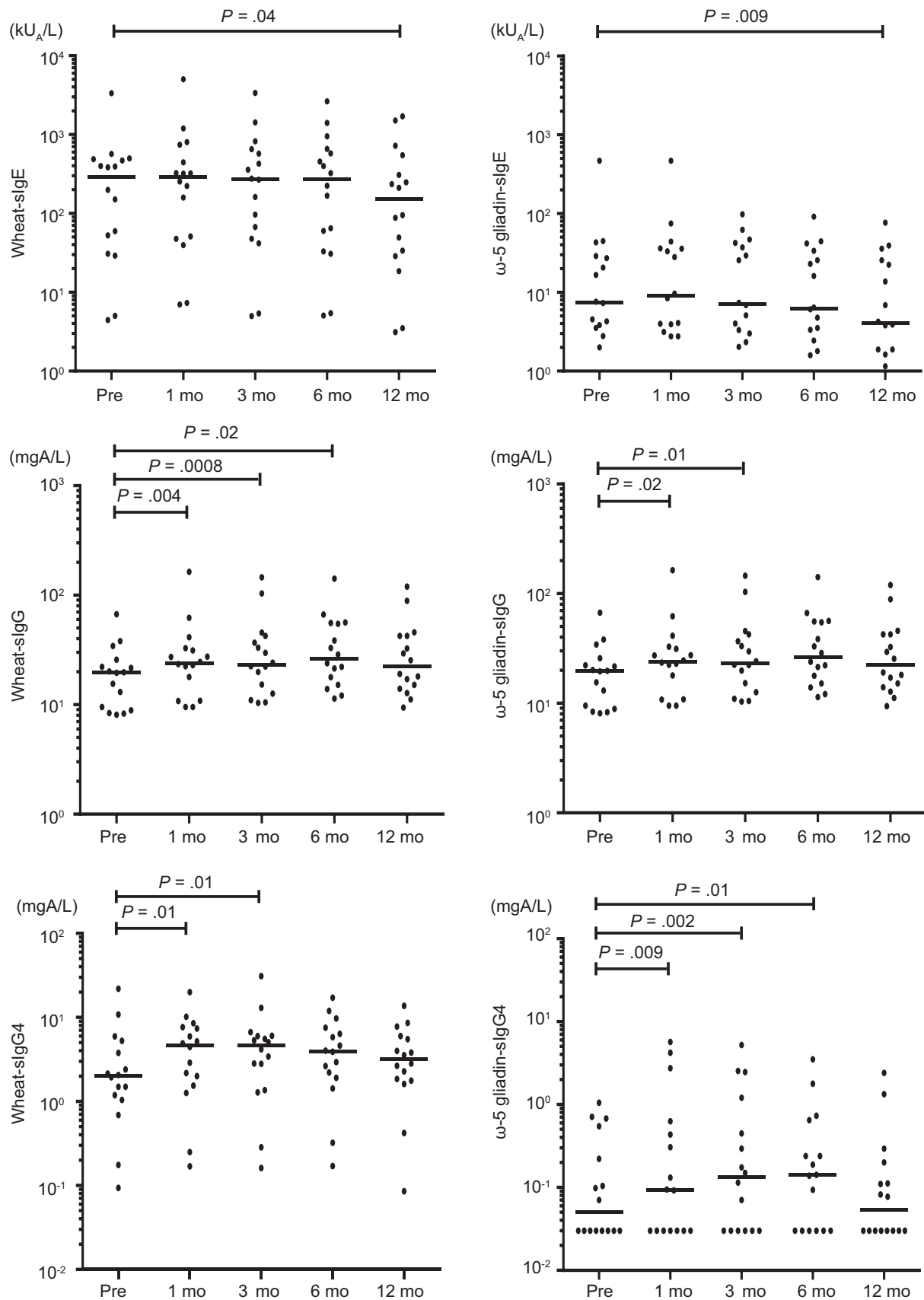
at-home doses taken over 2 years, the rate of symptoms requiring treatment was 2.6% and of symptoms requiring β_2 -stimulant inhalation was 1.7%. Furthermore, 3 of 18 patients received intramuscular adrenaline.¹² Pacharn et al conducted a wheat OIT for 2 patients, both of whom received adrenaline during the OIT protocol, for a total of 6 adrenaline injections.¹⁵ During the current study, the frequency of adverse symptom requiring treatment and β_2 -stimulant inhalation at home was 1.4% and 0.7%, respectively, which were lower than those in our previous study with a target dose of 5200 mg.¹² Seven anaphylaxis reactions were indicated for adrenaline auto-injector use,^{23,24} but not administered at the parents' discretion. Therefore, low-dose OIT was safer than those in previous reports regardless of allergy-related characteristic similarities among cohorts (high level of sIgE and anaphylactic episodes). The reason for the difference in ω -5 gliadin-sIgE level compared to RCT in the United States¹³ warrants further study.

The current study reported the reduction of wheat- and ω -5 gliadin-sIgE and the elevation of wheat- and ω -5 gliadin-sIgG and -sIgG₄ during low-dose OIT. In several trials, the reduction of wheat-sIgE was reported during wheat OIT.^{12,28} However, these trials did not assess ω -5 gliadin-sIgE. In the present study, we showed that wheat- and ω -5 gliadin-sIgE significantly decreased after 1 year. Additionally, we first demonstrated that wheat- and ω -5 gliadin-sIgG and ω -5 gliadin-sIgG₄ significantly increased after 1 month from baseline. Interestingly, these immunologic changes followed low-dose OIT. Although the rate of reduction of sIgE was mild compared to full-dose OIT, our study revealed that low-dose OIT can still induce immunologic changes. sIgG and sIgG₄ significantly increased at 1 and 3 months from the start of OIT and then gradually decreased. These findings are similar to those obtained from low-dose OIT for egg, milk, and peanut allergies, while high sIgG and IgG₄ levels were maintained during high-dose OIT.^{10,17-19}

One limitation of this study is that it is not an RCT. Because many facilities perform OIT in Japan, we were unable to establish a strict control group. To address this issue, we established a historical control group. Although there were no significant differences in patient characteristics between the two groups, there might be unknown confounding factors.

The second limitation was that we did not conduct full-dose OFC (2600-5200 mg of wheat protein). Because we performed low-dose OIT for the prevention of anaphylaxis due to accidental exposure by contamination of processed products, we used 400-mg OFC, which is equivalent to a piece of cookie. Increasing the threshold to 400 mg would reduce the risk of developing symptoms from accidental exposure by contamination and may improve the quality of life.^{20,22}

The third limitation was that we assessed sustained unresponsiveness by OFC after avoidance for 2 weeks instead of 4 weeks or more. Although a 2-week avoidance to assess short-term unresponsiveness has been used in other OIT trials,^{10,12,17-19,29,30} sustained unresponsiveness is usually defined by OFC after elimination for 1 month or more.⁸ However, among patients who passed the OFC after a 2-week cessation of OIT and were allowed to ingest wheat in



These data were analyzed for all 16 patients in the OIT group.

FIGURE 4 Specific IgE, IgG, and IgG₄ changes in the OIT group. Wheat- and ω-5 gliadin-specific IgE levels significantly decreased after 12 months from baseline. OIT: oral immunotherapy; sIgE: specific IgE; sIgG: specific IgG; sIgG₄: specific IgG₄

daily life, 60% did not report the experience of any symptoms during the questionnaire survey.²⁷ Therefore, risk of anaphylaxis would be low in patients who were able to consume 400 mg after 2 weeks of avoidance.²⁷

In conclusion, low-dose OIT safely achieved low-dose desensitization and induced immunologic changes for patients with wheat anaphylaxis.

ACKNOWLEDGMENTS

This study was supported by the Health and Labor Sciences Research Grants for Research on Allergic Disease and Immunology from the Ministry of Health, Labor, and Welfare of Japan (Motohiro Ebisawa, Grant number: 201414009A) and the Practical Research Project for Allergic Disease and Immunology from the Japan Agency for Medical Research and Development (AMED, 17ek0410019h0003).

CONFLICT OF INTEREST

Motohiro Ebisawa serves on the clinical medical advisory board of DBV Technologies and has received lecturing fees from Mylan EPD. The other authors declare that they have no conflicts of interest.

AUTHOR CONTRIBUTIONS

Ken-ichi Nagakura and Motohiro Ebisawa formulated the research hypothesis. Ken-ichi Nagakura corrected the data and drafted the manuscript. Noriyuki Yanagida, Sakura Sato, and Motohiro Ebisawa designed the study and critically reviewed the manuscript. Makoto Nishino, Kyohei Takahashi, Tomoyuki Asaumi, and Kiyotake Ogura recruited the research subjects and critically reviewed the manuscript.

DATA AVAILABILITY STATEMENT

The datasets used to support the findings of this study are available from the corresponding author, upon reasonable request.

ORCID

Ken-ichi Nagakura  <https://orcid.org/0000-0002-9381-9044>

Kyohei Takahashi  <https://orcid.org/0000-0003-1220-7386>

Tomoyuki Asaumi  <https://orcid.org/0000-0002-7464-5421>

Motohiro Ebisawa  <https://orcid.org/0000-0003-4117-558X>

REFERENCES

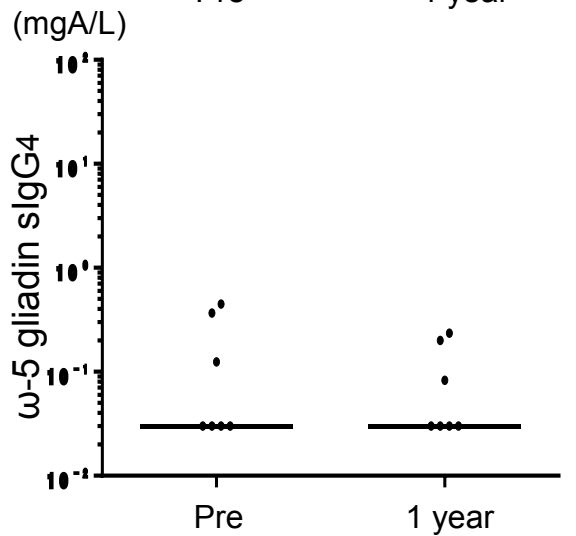
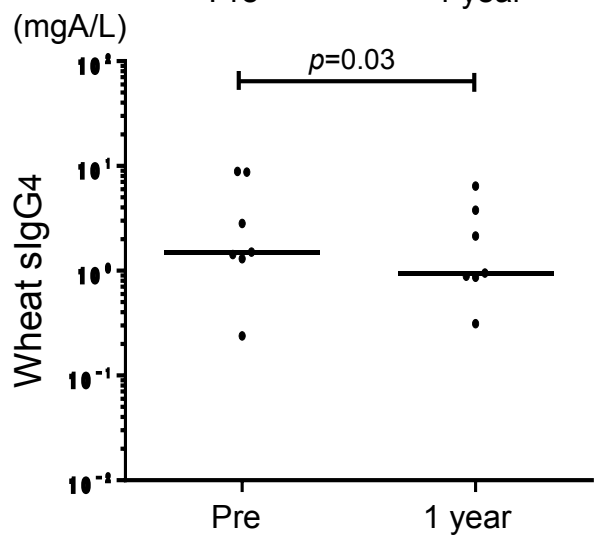
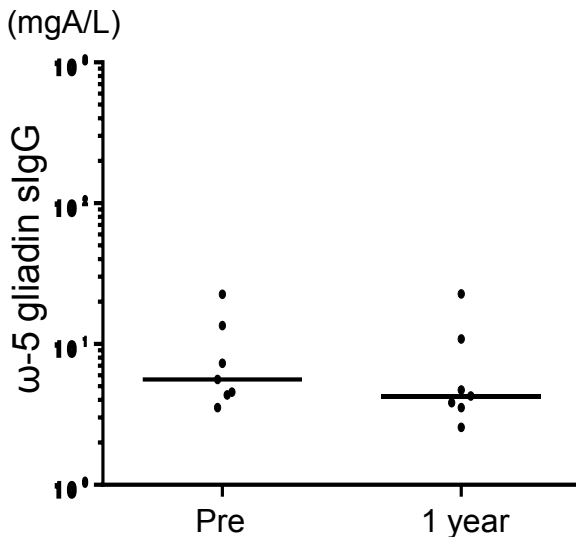
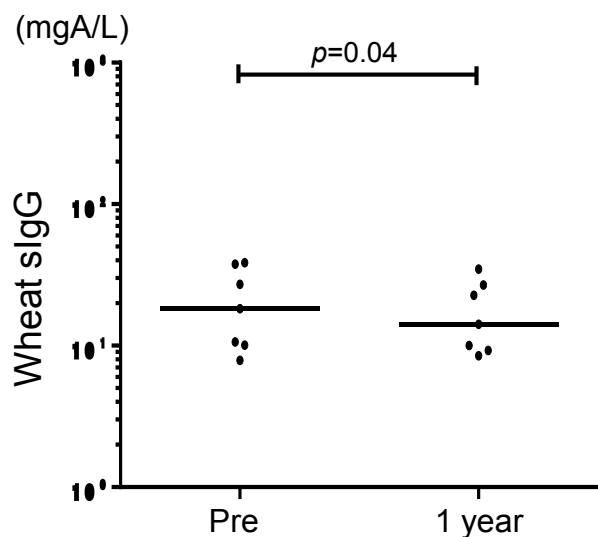
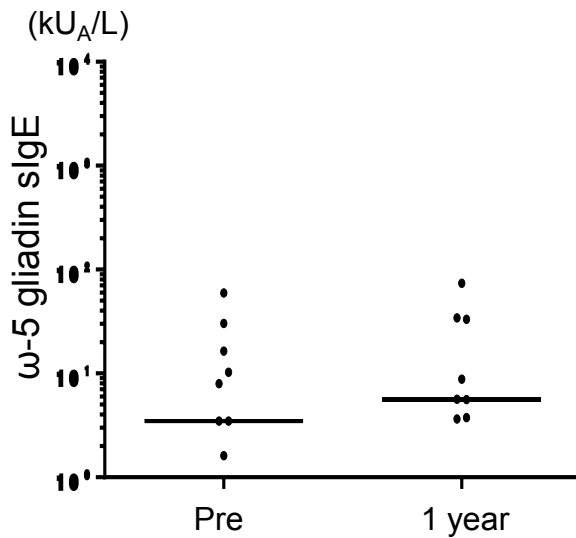
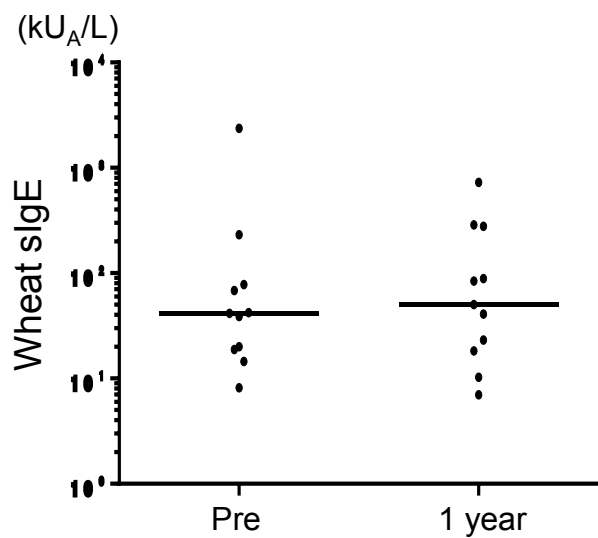
- Chafen JJ, Newberry SJ, Riedl MA, et al. Diagnosing and managing common food allergies: A systematic review. *JAMA*. 2010;303:1848-1856.
- Poole JA, Barriga K, Leung DY, et al. Timing of initial exposure to cereal grains and the risk of wheat allergy. *Pediatrics*. 2006;117:2175-2182.
- Akiyama H, Imai T, Ebisawa M. Japan food allergen labeling regulation—history and evaluation. *Adv Food Nutr Res*. 2011;62:139-171.
- Koike Y, Yanagida N, Sato S, et al. Predictors of persistent wheat allergy in children: A retrospective cohort study. *Int Arch Allergy Immunol*. 2018;176:249-254.
- Keet CA, Matsui EC, Dhillon G, Lenehan P, Paterakis M, Wood RA. The natural history of wheat allergy. *Ann Allergy Asthma Immunol*. 2009;102:410-415.
- Cianferoni A, Khullar K, Saltzman R, et al. Oral food challenge to wheat: A near-fatal anaphylaxis and review of 93 food challenges in children. *World Allergy Organ J*. 2013;6:14.
- Pajno GB, Fernandez-Rivas M, Arasi S, et al. EAACI Guidelines on allergen immunotherapy: IgE-mediated food allergy. *Allergy*. 2018;73:799-815.
- Wood RA. Food allergen immunotherapy: Current status and prospects for the future. *J Allergy Clin Immunol*. 2016;137:973-982.
- Nagakura KI, Sato S, Yanagida N, Ebisawa M. Novel immunotherapy and treatment modality for severe food allergies. *Curr Opin Allergy Clin Immunol*. 2017;17:212-219.
- Nagakura KI, Sato S, Yanagida N, et al. Oral immunotherapy in Japanese children with anaphylactic peanut allergy. *Int Arch Allergy Immunol*. 2018;175:181-188.
- Vazquez-Ortiz M, Alvaro M, Piquer M, et al. Baseline specific IgE levels are useful to predict safety of oral immunotherapy in egg-allergic children. *Clin Exp Allergy*. 2014;44:130-141.
- Sato S, Utsunomiya T, Imai T, et al. Wheat oral immunotherapy for wheat-induced anaphylaxis. *J Allergy Clin Immunol*. 2015;136(4):1131-1133.e7.
- Nowak-Węgrzyn A, Wood RA, Nadeau KC, et al. Multicenter, randomized, double-blind, placebo-controlled clinical trial of vital wheat gluten oral immunotherapy. *J Allergy Clin Immunol*. 2019;143:651-661.
- Lauener R, Eigenmann PA, Wassenberg J, et al. Oral immunotherapy with partially hydrolyzed wheat-based cereals: A pilot study. *Clin Med Insights Pediatr*. 2017;11:1179556517730018.
- Pacharn P, Siripipattanamongkol N, Veskitkul J, Jirapongsananuruk O, Visitsunthorn N, Vichyanond P. Successful wheat-specific oral immunotherapy in highly sensitive individuals with a novel multi-rush/maintenance regimen. *Asia Pac Allergy*. 2014;4:180-183.
- 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.
- 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.
- 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.
- Nagakura KI, Yanagida N, Sato S, et al. Low-dose oral immunotherapy for children with anaphylactic peanut allergy in Japan. *Pediatr Allergy Immunol*. 2018;29:512-518.
- Blumchen K, Trendelenburg V, Ahrens F, et al. Efficacy, safety, and quality of life in a multi-center, randomized, placebo-controlled trial of low-dose peanut oral immunotherapy in peanut allergic children. *J Allergy Clin Immunol Pract*. 2019;7:479-491.
- 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.
- Baumert JL, Taylor SL, Koppelman SJ. Quantitative assessment of the safety benefits associated with increasing clinical peanut thresholds through immunotherapy. *J Allergy Clin Immunol Pract*. 2018;6:457-465.
- Simons FE. Anaphylaxis. *J Allergy Clin Immunol*. 2010;126:885.
- Simons FE, Arduzzo LR, Bilò MB, et al. World allergy organization guidelines for the assessment and management of anaphylaxis. *World Allergy Organ J*. 2011;4:13-37.
- Sato S, Sugizaki C, Yanagida N, Ito K, Ohshima Y, Shimojo N. Questionnaire-based survey of oral immunotherapy in Japan. *Allergol Int*. 2018;67:399-404.

26. Ebisawa M, Ito K, Fujisawa T. Japanese guidelines for food allergy 2017. *Allergol Int.* 2017;66:248-264.
27. Manabe T, Sato S, Yanagida N, et al. Long-term outcomes after sustained unresponsiveness in patients who underwent oral immunotherapy for egg, cow's milk, or wheat allergy. *Allergol Int.* 2019;68:527-528.
28. Rekabi M, Arshi S, Bermanian MH, et al. Evaluation of a new protocol for wheat desensitization in patients with wheat-induced anaphylaxis. *Immunotherapy.* 2017;9:637-645.
29. Blumchen K, Ulbricht H, Staden U, et al. Oral peanut immunotherapy in children with peanut anaphylaxis. *J Allergy Clin Immunol.* 2010;126(1):83-91.e1.
30. Hsiao KC, Ponsonby AL, Axelrad C, Pitkin S, Tang MLK, PPOIT Study Team. Long-term clinical and immunological effects of probiotic and peanut oral immunotherapy after treatment cessation: 4-year follow-up of a randomised, double-blind, placebo-controlled trial. *Lancet Child Adolescent Health.* 2017;1:97-105.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Nagakura K-I, Yanagida N, Sato S, et al. Low-dose-oral immunotherapy for children with wheat-induced anaphylaxis. *Pediatr Allergy Immunol.* 2020;00:1-9. <https://doi.org/10.1111/pai.13220>



Supplementary Information

Supplementary Table 1. Grading of the severity of adverse symptoms

	1 (Mild)	2 (Moderate)	3 (Severe)
Skin	Localized hives, exanthema, wheal, pruritus	Generalized hives, exanthema, wheal, pruritus	-
	Swollen eyelid or lip	Swollen face	-
Gastrointestinal tract	Pruritus of the throat or oral cavity	Throat pain	-
	Mild abdominal pain	Moderate abdominal pain	Cramps
	Nausea, emesis, diarrhea	Recurrent emesis, diarrhea	Continuous emesis, loss of bowel control
Respiratory tract	Intermittent cough, nasal congestion, sneezing, rhinorrhea	Repetitive cough	Persistent cough, hoarseness, “barky” cough
	-	Chest tightness, wheezing detectable via auscultation	Audible wheezing, dyspnea, cyanosis, oxygen saturation <92%, swallowing or speaking difficulties, throat tightness, respiratory arrest
Cardiovascular	-	Pale face, mild hypotension, tachycardia (increase >15 beats/min)	Hypotension, dysrhythmia, severe bradycardia, cardiac arrest
Neurological	Change in activity level, lethargy	“Light-headedness,” feeling of “impending doom,”	Confusion, loss of consciousness, incontinence

somnolence, headache

The severity score was based on the organ system that showed the most severe reactions. Hypotension was defined as systolic blood pressure of <70 mmHg for children aged 1 month to 1 year, $<70 + (2 \times \text{age})$ mmHg for children aged 1–10 years, and <90 mmHg for children aged >11 years. Mild hypotension was defined as systolic blood pressure of <80 mmHg for children aged 1 month to 1 year, $<80 + (2 \times \text{age})$ mmHg for children aged 1–10 years, and <100 mmHg for children aged >11 years. Wheezing detectable via auscultation with a stethoscope was defined as mild. Audible wheezing was defined as wheezing detected without a stethoscope.

Supplementary Table 2. Dosing schedule of OIT

Step	Wheat protein (mg)	Udon noodles (g)
1	2.7	0.1
2	5.3	0.2
3	8.0	0.3
4	13.3	0.5
5	18.6	0.7
6	26.5	1.0
7	39.8	1.5
8	53.0	2.0

OIT: oral immunotherapy

The quantitative value of wheat protein was measured via the Kjeldahl method.

In addition, if no symptoms at all or only mild symptoms occurred, the amount of wheat protein ingested the next day was increased by 1 step. If moderate or severe symptoms appeared, the next day's dose was the same or decreased by 1 step, respectively.

2g of boiled udon noodle is equivalent to 5 cm of boiled udon noodle.