

Clinical Communications

Long-term prognosis after wheat oral immunotherapy

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Clinical Implications

- An allergic reaction after wheat oral immunotherapy is not rare. Performing exercise after wheat intake was found to be the main trigger that evoked symptoms; therefore, long-term follow-up for patients is necessary.

TO THE EDITOR:

Wheat is a major causative allergen of immediate allergic reactions and the third most common food allergen in Japan.¹ The reported number of patients who have undergone wheat oral immunotherapy (OIT) is less than that of patients who have undergone peanut, egg, or milk OIT.²⁻⁴ Previously, we reported on the short-term efficacy of wheat OIT for wheat-induced anaphylaxis.³ In that study, 18 patients with wheat anaphylaxis underwent wheat OIT for 2 years. Subsequently, 11 patients (61.1%) passed a final oral food challenge (OFC, 5200 mg of

wheat protein) after OIT cessation at 2 weeks. However, no follow-up report was undertaken after the patients had received wheat OIT.

This study aimed to evaluate the long-term prognosis for patients who received wheat OIT, and to identify risk factors associated with induced symptoms.

Patients with wheat anaphylaxis underwent wheat OIT according to the prescribed protocol (Figure E1, available in this article's Online Repository at www.jaci-inpractice.org) between March 2010 and March 2013. A final OFC involving the consumption of 200 g of boiled udon noodles (5200 mg wheat protein) was performed after a 2-week period of complete wheat avoidance. Patients who had passed the final OFC were able to maintain the threshold (>5200 mg wheat protein) for at least 2 weeks; therefore, they were permitted to consume wheat products in their daily meals throughout the long-term follow-up period (Figure E2, available in this article's Online Repository at www.jaci-inpractice.org). We evaluated wheat-induced reactions and the patients' clinical presentation over a 2-year follow-up period after the final OFC. We compared patient characteristics and immunological parameters among symptomatic and asymptomatic patient groups.

The study participants comprised 19 of 44 patients with wheat OIT. Table I shows the patient characteristics, and Table E1 (available in this article's Online Repository at www.jaci-inpractice.org) shows the frequency of symptoms in OIT.

TABLE I. Comparison of patient characteristics in the symptomatic and asymptomatic groups

	Total (n = 19)	Symptomatic group (n = 8)	Asymptomatic group (n = 11)	P value
Sex (male:female)	13:6	6:2	7:4	>.999
Age, y, median (IQR)				
At baseline OFC	8.9 (7.1-10.7)	7.2 (6.8-9.5)	9.5 (8.5-10.7)	.200
At final OFC	10.6 (8.7-11.5)	9.1 (8.5-11.5)	11.2 (9.8-11.5)	.386
Symptom threshold dose at baseline DBPCFC (wheat protein), g, median (IQR)	0.08 (0.08-0.32)	0.2 (0.08-0.32)	0.08 (0.08-0.38)	.759
Complication at baseline OFC, n (%)				
Atopic dermatitis	12 (63)	6 (75)	6 (55)	.633
Bronchial asthma	12 (63)	5 (63)	7 (64)	>.999
Allergic rhinitis	10 (53)	4 (50)	6 (55)	>.999
Period between baseline OFC and final OFC passed, d, median (IQR)	506 (286-680)	506 (437-726)	388 (198-648)	.200
Wheat-specific IgE, kUA/L				
At baseline OFC	80 (31.3->100)	90.5 (69.57->100)	60.9 (23.75->100)	.407
At final OFC	43.5 (21.7-74.5)	51.1 (32.47-94.32)	28.1 (17.7-28.9)	.264
After OIT	27.7 (17.0-59.5)	37.0 (23.02-79.0)	19.2 (16.55-42.7)	.173
ω-5 gliadin-specific IgE, kUA/L				
At baseline OFC	3.43 (1.7-7.12)	3.25 (1.9-13.6)	4.3 (0.66-5.89)	.413
At final OFC	0.96 (0.3-1.93)	1.15 (0.3-5.24)	0.96 (0.49-1.38)	.568
After OIT	0.59 (0.19-0.92)	0.40 (0.19-2.49)	0.71 (0.15-0.92)	.803
Wheat SPT wheal size, mm				
At baseline OFC	8 (5-10)	8 (3-13)	8 (5-10)	>.999
At final OFC	6 (4-10)	7 (5-12)	5 (3-9)	.198
After OIT	8 (3-10)	9 (8-15)	5 (2-7)	.168

DBPCFC, Double blind placebo-controlled food challenge; IQR, interquartile range; OFC, oral food challenge; OIT, oral immunotherapy; SPT, skin prick test.

Data are presented as median (25-75 percentiles) or n (%).

Differences were evaluated using the Mann-Whitney test for continuous variables or Fisher's exact test for categorical variables.

TABLE II. Details concerning symptomatic patients

Patient	Age, y	Sex	Symptom	Anaphylaxis	Culprit food	Exercise at the onset	Time between wheat ingestion and exercise/symptoms	Period after the final OFC, mo	Treatment	Frequency of ingestion of wheat after final OFC, d/wk	
										Staple foods*	Products*
1	14	M	Audible wheezing, swollen eyelids and lips	+	Croquette (fried mashed potato)	Running	30 min	11	Antihistamine and steroid injection beta-2 stimulant inhalation	1	NA
2	9	M	Generalized urticaria, persistent cough, dyspnea	+	Gyoza (boiled dumplings)	Walking	15 min	10	Adrenaline autoinjection, beta-2 stimulant inhalation	1	3-6
3	15	M	Abdominal pain	—	Pork cutlet	—	—	13	No treatment	0-1	0-1
4	8	M	Localized urticaria, wheezing detectable via auscultation	—	Pasta	Running	1 h	1	Antihistamine formulation	7	7
5	11	F	Localized urticaria, swollen eyelids	—	Yakisoba (stir-fried noodles)	Dancing	1.5 h	8	Antihistamine formulation	NA	NA
6	9	M	Generalized urticaria, audible wheezing	+	Processed food containing wheat	Running	NA	1	Adrenaline autoinjection	1-2	3-6
7	7	F	Localized urticaria, repetitive cough	—	Pasta	Running	1 h	1	Antihistamine formulation	3-6	3-6
8	9	F	Repetitive cough	—	Udon (wheat noodles)	—	—	11	Beta-2 stimulant inhalation	3-6	7

NA, Not available; OFC, oral food challenge.

*Staple foods are bread, pasta, udon noodles, and other foods. Products include cookies, food using breadcrumbs, gyoza (Japanese dumplings), and other foods.

After the final OFC, 3 (16%), 7 (37%), and 8 (42%) patients experienced symptoms within 1 month, 12 months, and 2 years, respectively (Figure E3, available in this article's Online Repository at www.jaci-inpractice.org).

Table II shows the details of 8 patients who became symptomatic after the OIT. These patients experienced skin, gastrointestinal tract, and respiratory symptoms, and 3 patients developed anaphylaxis.

Regarding symptom onset, 5 patients developed symptoms during physical exercises such as running and dancing, 1 patient became symptomatic while walking, and 2 patients were symptomatic at rest. Seven patients required medical treatment, and 2 patients received an intramuscular injection of adrenaline. Regarding the intake frequency of wheat after the final OFC, patients who consumed wheat daily and those who consumed wheat between 0 and 1 times per week were included. Doctors instructed these patients to increase their wheat consumption frequency, to refrain from exercising after wheat ingestion, and to resume low-dose wheat consumption.

When comparing the symptomatic and asymptomatic groups, there was no significant difference in sex, age, history of anaphylaxis, symptom threshold dose of wheat before OIT, complications of allergic disease, and the time between starting OIT and the final OFC. There was no significant difference in wheat- and $\omega 5$ gliadin-sIgE (kU_A/L) values and wheat skin prick test wheal size between the 2 groups at the baseline OFC, the final OFC, and at 6 to 13 months after the final OFC (Table I). Wheat- and $\omega 5$ gliadin-sIgE values (kU_A/L) showed a significant decrease over time in both groups (Figure E4, available in this article's Online Repository at www.jaci-inpractice.org). There were no significant differences in the frequency of symptoms and treatments per patient between the 2 groups during the rush phase, the long-term build-up phase, and the maintenance phase of OIT (Tables E2 and E3, available in this article's Online Repository at www.jaci-inpractice.org).

Long-term follow-up studies on OIT for egg and milk allergies have been undertaken.^{5,6} Our study is the first to investigate the long-term prognosis of patients who received wheat OIT rather than using a questionnaire survey on the prognosis after egg, milk, or wheat OIT.⁷

After passing the final OFC, 8 of 19 patients (42.1%) showed adverse allergic reactions during the 2-year follow-up period, and their symptoms were not always mild. When comparing symptomatic and asymptomatic patients, there was no significant difference in patient background, sIgE values, and the frequency of symptoms and treatments during OIT. It is difficult to estimate the risk of symptoms after OIT; therefore, long-term follow-up after wheat OIT is necessary.

In our study, 6 of 8 patients developed symptoms during exercise. Kusunoki et al⁸ reported on a child with wheat allergy who developed an exercise-related anaphylactic reaction after wheat ingestion after desensitization using OIT. Our study findings were similar and showed that some patients who had passed the full-dose OFC after wheat avoidance for 2 weeks experienced exercise-related allergic reactions after wheat OIT.

Exercise after wheat intake was the main trigger for evoking the symptoms. Therefore, long-term follow-up of patients should include assessments for exercise-induced allergic symptoms after OIT.

In one study, peanut OIT did not improve the frequency of induced symptoms and quality of life compared with avoiding peanuts.⁹ However, no similar report has been published concerning wheat, which is used frequently in staple foods, such as bread and udon, and in other processed products in Japan.

After having undergone wheat OIT, more than 50% of patients were asymptomatic for 2 years. We consider that wheat OIT may have a certain efficacy in clinical practice when treating wheat allergy. However, owing to the risk of induced symptoms associated with exercise, its usefulness may be limited. In the future, it is necessary to consider what kind of OIT is effective and safe.

This study has one limitation. The 2-week period of wheat avoidance before the final OFC was relatively short. However, in daily life, not consuming wheat for more than 2 weeks is rare, and most patients had no problems consuming wheat as a staple food at least once a week, even after OIT.

We found that exercise-related allergic reactions after wheat OIT were not rare, and it was difficult to estimate the risk of symptoms after OIT. Therefore, long-term follow-up after OIT is necessary and, particularly, should include assessment of exercise-induced allergic symptoms.

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ONLINE REPOSITORY

Double blind placebo-controlled food challenge (DBPCFC)

The oral food challenge (OFC) was conducted via the DBPCFC on admission. The study patients were informed that oral antihistamines and oral steroids had been discontinued before the DBPCFC. The trial food was 15 g of white sorghum (placebo) and 16 g of wheat flour (wheat protein content, 1.3 g), which were masked in a cake using pumpkin and sugar. The cake was heated at 1000 W for 90 seconds. The test was performed after confirming that the patients were not allergic to either pumpkin or white sorghum. The trial food target was 1.3 g of wheat protein; patients consumed the trial food every 15 minutes. The OFC was discontinued when objective moderate or severe symptoms developed (generalized urticaria, continuous coughing, moderate abdominal pain, vomiting, and diarrhea). If mild subjective symptoms (pruritus of the throat or oral cavity, or mild abdominal pain) or mild objective symptoms (localized urticaria or intermittent coughing) appeared during the OFC, patients were carefully monitored to detect any worsening of symptoms, and the OFC was continued after informed consent was obtained from the child's legal guardian.

Protocol for wheat OIT

Preparation of OIT trial food. The OIT trial food was boiled udon (250 g of frozen udon noodles cooked in 100°C water for 1 minute). During the rush phase, the investigator weighed the boiled udon noodles cooked at the hospital using a scale, as did the parents at home. The rush-phase OIT was conducted under careful observation by doctors during a 5-day admission of the study patients. Three days before admission, patients were administered oral antihistamines (loratadine) and leukotriene receptor antagonists (montelukast) to alleviate symptoms. On the first day of admission, we performed the second baseline OFC using an open challenge to confirm the threshold of objective symptoms. The first dose was the same as the threshold dose of objective symptoms on the first day. The dose was increased at 5-hour intervals twice a day and was stepped up or down on the basis of the severity of the adverse reaction.

Long-term build-up and maintenance phase. On the fifth day, the rush-phase OIT was complete and the long-term build-up and maintenance phases were started at home. During the long-term build-up phase, the dose was increased to the target dose of 5.2 g of wheat protein in 0.13 g increments every week at home. In the event of an adverse reaction, the dose was maintained and repeated or reduced according to the severity of the adverse reaction. If the dose was tolerated, it was increased again. If a patient reached the target dose and did not develop any symptoms, orally administered loratadine and montelukast

were discontinued. The patient was then permitted to increase the amount of processed foods in his or her daily diet, provided the food item contained less than 0.65 g of wheat protein and he or she remained asymptomatic for another month. To prepare for adverse reactions during OIT, we educated the patients and their legal guardians on the treatment methods to use when symptoms developed. All patients were prescribed antihistamines, oral steroids, inhaled β_2 agonists, and adrenaline auto-injectors (Epipen). The emergency medicine systems included a 24-hour helpline operated by staff from our hospital. Patients who lived far from the hospital could be referred to and examined at an appropriate emergency location determined in advance.

The methodology used in this study was derived from Sato et al's 2015 study methodology.³

Outcomes, patients' characteristics, and immunological parameters. We retrospectively evaluated the wheat-induced reactions and the clinical presentation of the study patients over a 2-year period after the final OFC. We compared patient characteristics (symptom threshold dose and serum specific IgE [sIgE] values) at baseline OFC, the progression of OIT (frequency of associated symptoms and treatment, and sIgE values), and the sIgE values after OIT among the symptomatic and asymptomatic groups. Each OIT-induced symptom was evaluated, and treatment was administered using the Japanese guidelines for food allergy.¹

Regarding immunological parameters, wheat- and ω 5-gliadin-sIgE values were evaluated at the baseline OFC, the final OFC, and 6 to 13 months after the final OFC. The sIgE values were measured using the Immuno CAP assay system (Thermo Fisher Scientific, Uppsala, Sweden). A skin prick test was performed using wheat extract (Torii Pharmaceutical, Tokyo, Japan), and the sIgE was measured.

Ethical considerations

In accordance with the Declaration of Helsinki, the study design and the risks of symptom provocation were fully explained to the patients and the children's guardians both verbally and in writing. Written informed consent was obtained from the guardians before participation. The study design was approved by the Institutional Review Board of Sagami National Hospital (Approval No. 2008-17).

Statistical analysis

We determined patient profiles using patient age, the level of the specific IgE, and the skin prick test wheal diameter, and they were represented using median values. For statistical comparisons between the 2 groups, we used Mann-Whitney *U* tests for continuous variables and Fisher's exact tests for categorical variables. *P* values <.05 were considered significant.

All data were statistically analyzed using SPSS version 24 (IBM, Armonk, NY).

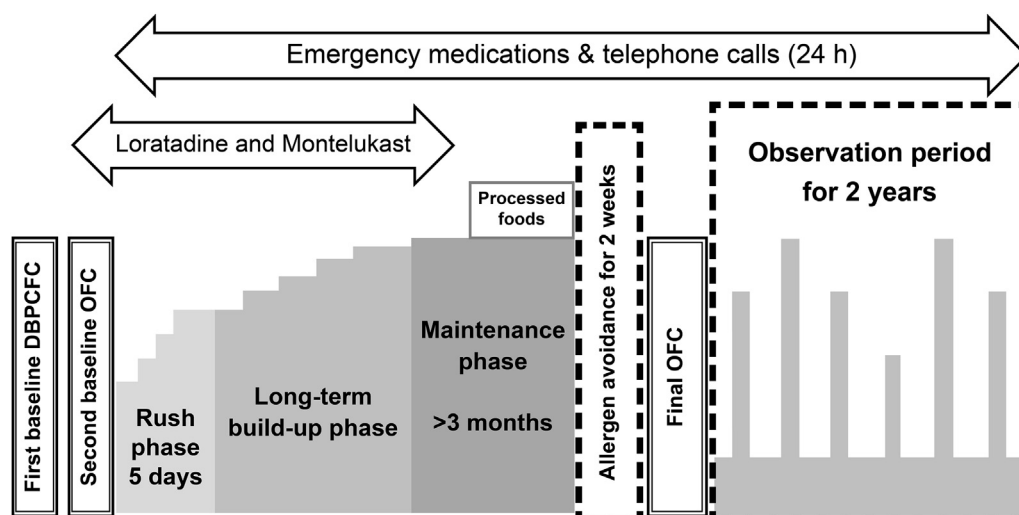


FIGURE E1. OIT protocol. The rush phase was performed in the hospital, and the long-term build-up and maintenance phases were continued at home. The final OFC was performed to confirm sustained unresponsiveness after 2 weeks of complete wheat avoidance. The patients who passed the final OFC started to consume wheat freely. *OFC*, Oral food challenge; *OIT*, oral immunotherapy.

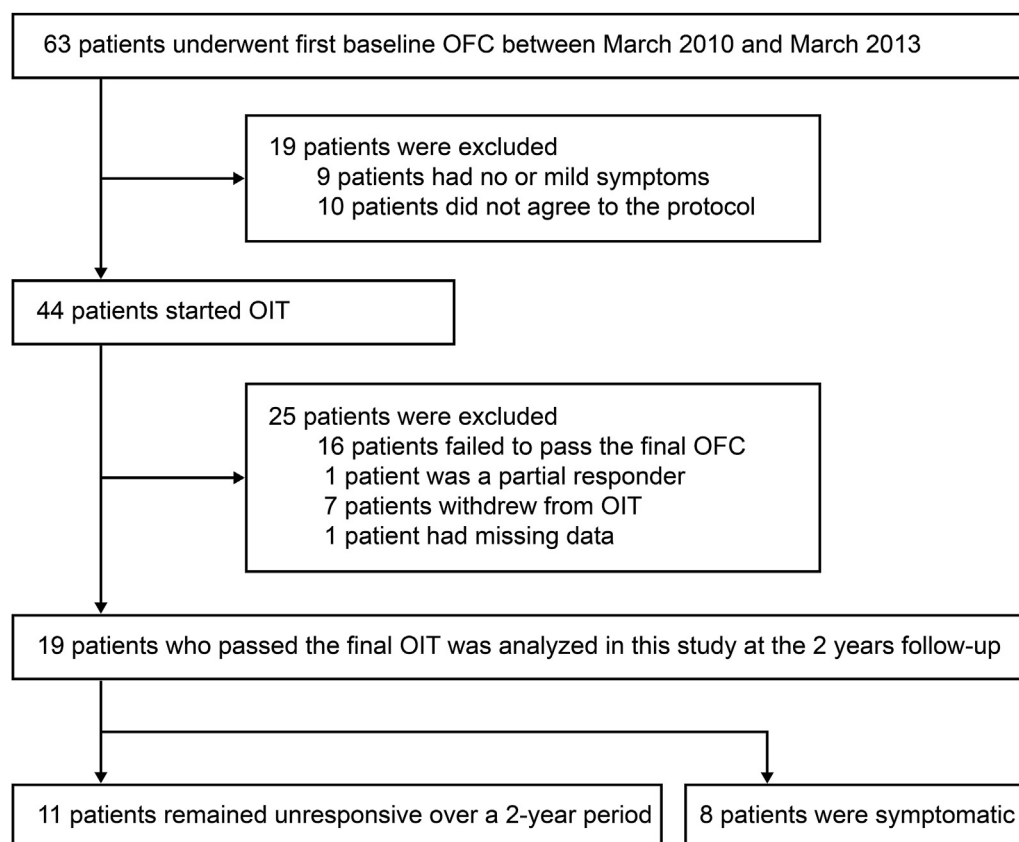


FIGURE E2. Study enrollment and outcomes. *OFC*, Oral food challenge; *OIT*, oral immunotherapy.

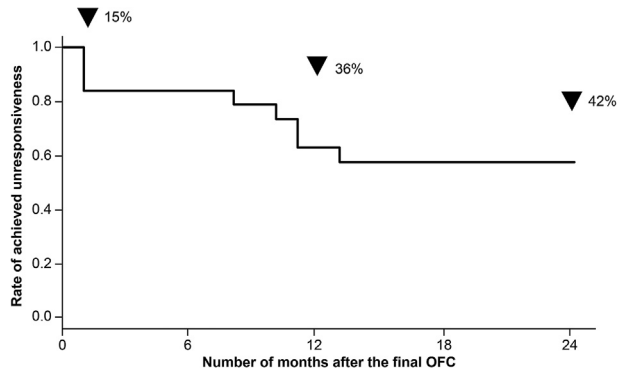


FIGURE E3. Changes in the rate of achieved unresponsiveness.
OFC, Oral food challenge.

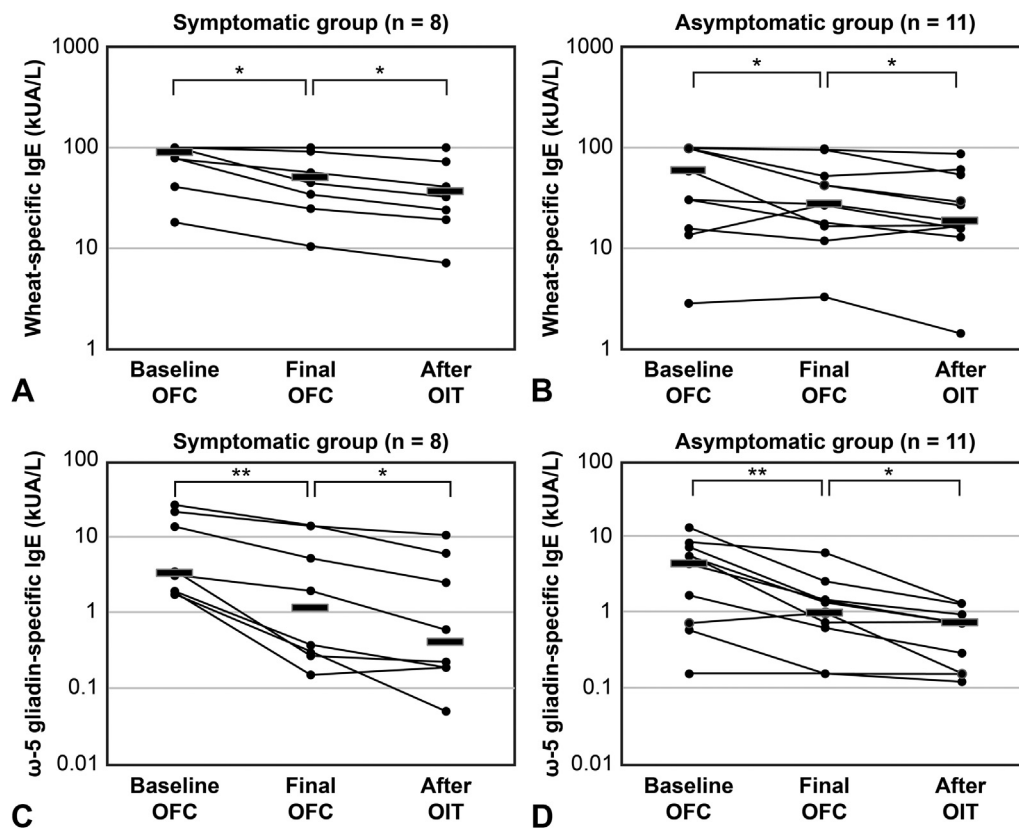


FIGURE E4. A comparison of immunological parameters in the symptomatic and asymptomatic groups. Wheat- and ω-5-gliadin-sIgE values were evaluated at the baseline OFC, the final OFC, and at 6-13 months after the final OFC. Wheat- and ω-5-gliadin-sIgE (kUA/L) levels significantly decreased over time in both groups. *OFC*, Oral food challenge; *OIT*, oral immunotherapy.

TABLE E1. Adverse allergic reactions and treatment during the OIT protocol

Adverse reactions and treatments (n = 19)	Long-term build-up and maintenance phase	
	Rush phase	
Total no. of intakes of OIT	8 (7-8)	327 (110-673)
Adverse reactions, total, %	14.2 (0-100)	3.9 (0.4-12.0)
Severity of symptoms, %		
Mild	12.5 (0-85.7)	2.7 (0-10.7)
Moderate	0 (0-25.0)	0.5 (0-3.0)
Severe	0 (0-0)	0 (0-01.8)
Organ-specific symptoms, %		
Skin	12.5 (0-62.5)	0.8 (0-6.1)
Mucosal	0 (0-100)	0.4 (0-4.9)
Gastrointestinal tract	0 (0-50.0)	0.4 (0-8.8)
Respiratory	0 (0-37.5)	1.3 (0-6.9)
Cardiovascular	0 (0-0)	0 (0-0)
Treatments, %		
Total	0 (0-50.0)	0.8 (0-5.3)
Use of antihistamine oral or IV	0 (0-50.0)	0.3 (0-2.7)
Use of steroid oral or IV	0 (0-12.5)	0 (0-0.9)
Use of beta 2-inhalation	0 (0-25.0)	0.2 (0-4.8)
Use of adrenaline IM	0 (0-0)	0 (0-0.2)

IM, Intramuscular; IV, intravenous; OIT, oral immunotherapy.

TABLE E2. Comparison of adverse allergic reactions and treatment during the rush phase among those who had symptoms vs those who had no symptoms

Adverse reactions and treatments	Symptom group (n = 8)	No-symptom group (n = 11)	P value
Total number of intakes of OIT	317 (220-633)	327 (110-673)	.600
Adverse reactions, total, %	3.4 (1.3-8.8)	4.2 (0.4-12.0)	.904
Severity of symptoms, %			
Mild	2.8 (1.1-8.8)	1.2 (0.6-10.7)	.772
Moderate	0.5 (0-2.2)	0.5 (0-3.0)	.933
Severe	0 (0-1.8)	0 (0-0.4)	.897
Organ-specific symptoms, %			
Skin	0.6 (0-3.6)	0.9 (0-6.1)	.710
Mucosal	0.3 (0-2.2)	0.4 (0-4.9)	.864
Gastrointestinal tract	0.5 (0-8.8)	0.4 (0-6.6)	.529
Respiratory	1.5 (0-3.7)	1.2 (0-6.9)	>.999
Cardiovascular	0 (0)	0 (0)	>.999
Treatments, %			
Total	0.9 (0-2.7)	0.2 (0-5.3)	.615
Use of antihistamine oral or IV	0.9 (0-2.3)	0.2 (0-2.7)	.668
Use of steroid oral or IV	0.4 (0-0.9)	0.1 (0-0.3)	.089
Use of beta 2-inhalation	0.2 (0-1.1)	0 (0-4.8)	.699
Use of adrenaline IM	0 (0-0)	0 (0-0.2)	.245

IM, Intramuscular; IV, intravenous; OIT, oral immunotherapy.

Data are percentage of doses with reaction/treatment per child, median (range).

Differences were evaluated using the Mann-Whitney test.

TABLE E3. Comparison of adverse allergic reactions and treatment during the long-term build-up and maintenance phase among those who had symptoms vs those who had no symptoms

Adverse reactions and treatments	Symptom group (n = 8)	No-symptom group (n = 11)	<i>P</i> value
Total no. of intakes of OIT	317 (220-633)	327 (110-673)	.600
Adverse reactions, total, %	3.4 (1.3-8.8)	4.2 (0.4-12.0)	.904
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Total	0.9 (0-2.7)	0.2 (0-5.3)	.615
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Use of steroid oral or IV	0.4 (0-0.9)	0.1 (0-0.3)	.089
Use of beta 2-inhalation	0.2 (0-1.1)	0 (0-4.8)	.699
Use of adrenaline IM	0 (0-0)	0 (0-0.2)	.245

IM, Intramuscular; *IV*, intravenous; *OIT*, oral immunotherapy.

Data are percentage of doses with reaction/treatment per child, median (range).

Differences were evaluated using the Mann-Whitney test.