Letter to the Editor

Wheat oral immunotherapy for wheat-induced anaphylaxis

To the Editor:

Wheat is the third most common causative antigen of anaphylaxis in Japan.[1] However, oral immunotherapy (OIT) can increase the threshold dose.[2,3] There are few reports on OIT in patients with anaphylaxis,[3,4] and there are even fewer that focus on wheat allergens.[5]

The aim of this study was to investigate the efficacy of OIT in patients with wheat-induced anaphylaxis. The primary end point of this study was *tolerance induction*, which was defined as sustained unresponsiveness from when OIT was discontinued until 2 years later.

Eighteen subjects with wheat anaphylaxis (11 boys and 7 girls; median age, 9.0 years) who underwent wheat OIT between June 2010 and July 2011 were recruited from Sagamihara National Hospital as an OIT group (see Table E1 and Fig E1, *A*, in this article's Online Repository at www.jacionline.org). OIT inclusion criteria for subjects were an age of at least 5 years, with anaphylaxis confirmed by double-blind placebo-controlled food challenge (DBPCFC). Exclusion criteria were poorly controlled bronchial asthma or atopic dermatitis and any other form of current immunotherapy. For the historical control group, we selected all subjects (8 boys and 3 girls; median age [range], 7.0 years [5.9-13.6]) who had definitive histories of anaphylaxis, excluding wheat-dependent, exercise-induced anaphylaxis, with more than a 2-year interval before oral food challenge (OFC) to wheat between September 2005 and July 2014 (see Table E1 and Fig E1, *B*). We could not have a control group more suitable than his historical control group due to the following reasons. Sagamihara National Hospital is known as a pivotal facility for food allergy practice throughout Japan, and thus many patients and their parents visit our clinic from all over the country. Most of these parents believe that OIT is the only curative therapeutic method and enthusiastically hoped to participate in the active group, although we endeavor to persuade the parents that OIT is part of a clinical trial that often requires a control group. Ethical approvals were obtained through the institutional review boards of Sagamihara National Hospital. Informed consent was obtained from all patients.

OIT was carried out in an open manner. We implemented OIT according to the study protocol (see Table E2 and Fig E2 in this article's Online Repository at www.jacionline.org). The rush phase was performed in the hospital, and the long-term build-up and maintenance phase was then continued at home. The target dose was 200 g of boiled udon (Japanese wheat noodles that included 5.2 g of wheat protein; Tablemark, Co, Ltd, Tokyo, Japan). If subjects were able to reach the target dose, the final OFC was performed after the cessation of OIT for 2 weeks—this OFC was conducted to confirm acquisition tolerance. Sera from subjects were analyzed for wheat-specific IgE (sIgE) and IgG_4 (sIgG4) using ImmunoCAP (Thermo Fisher Scientific, Inc, Uppsala, Sweden). The severity grading of symptoms was investigated and assigned 3 grades (see Table E3 in this article's Online Repository at www.jacionline.org).[6] In the historical control group, the definition of tolerance was

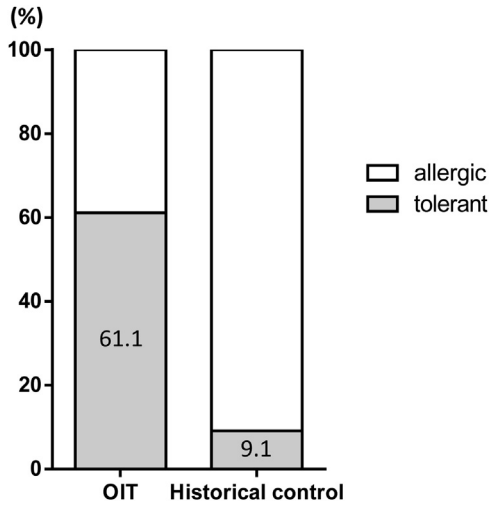

FIG 1. Comparison of outcome between OIT and control group in 2 years. The tolerance rate of the OIT group and the control group was determined as follows: tolerant (subject passed the final OFC), allergic (subject did not pass the final OFC in the OIT group or had an allergic reaction at the OFC or did not ingest the target amount of wheat in the control group). The *gray bar* represents the rate of tolerant subjects. The *white bar* represents the rate of allergic subjects.

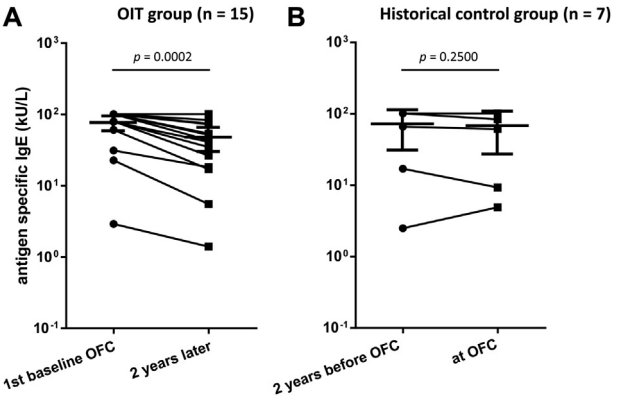

FIG 2. Changes in wheat-specific IgE level. Wheat-specific IgE level was measured using an immunoCAP instrument in the OIT group (n = 15) and the historical control group (n = 7). *P* value for the comparison between groups was calculated by using the Wilcoxon signed rank test.

that a subject could ingest 5.2 g of wheat protein daily after passing the OFC.

At first baseline DBPCFC, the median symptom threshold dose was 0.08 g (0.02-1.3 g) of wheat protein (Table E2). Seventeen subjects (94.4%) were classified as severe. Six subjects (35.3%) required intramuscular adrenaline, and 2 subjects (11.1%) went into anaphylactic shock.

During the rush phase, 17 subjects (94.4%) could ingest the target dose. Although 42 (26.4%) of the 143 total doses resulted in symptoms, no subjects required intramuscular adrenaline (see Table E4 in this article's Online Repository at www.jacionline.org). Subsequently, 2 subjects dropped out and were excluded from the analysis. A total of 16 subjects who continued OIT could

achieve the target dose and ingest it without symptoms (desensitization). Precisely, 486 (6.8%) of the 5778 total doses resulted in symptoms, with 1 use of intramuscular adrenaline. Finally, 11 subjects (61.1%) passed the final OFC within 2 years (tolerance). In the historical control group, the results of OFC were positive in 10 of the 11 subjects. The remaining subject was determined to have tolerance. The tolerance rates of the OIT group were significantly higher than those of the historical control group (61.1% vs 9.1%, respectively; $P = .008$) (Fig 1).

Wheat-sIgE in the OIT group reduced significantly during therapy (first baseline OFC, >100 kU/L [95% CI, 59.3-96.0] vs 2 years later, 43.5 kU/L [95% CI, 30.5-66.5]; $P = .0002$), whereas that of the historical control group was not significantly changed in 2 years (2 years before OFC, >100 kU/L [95% CI, 30.0-110.0] vs OFC, 83.5 kU/L [95% CI, 26.5-105.5]; $P = .25$) (see Fig 2). Wheat-sIgE in the OIT group did not show a statistically significant difference between tolerant and allergic subjects (data not shown).

Rodriguez del Rio et al[5] reported OIT for wheat in 4 of 6 children, although approximately 60% of the 4 developed tolerance within 2 years. In our own experiences using rush OIT for food-induced anaphylaxis, tolerance rates were 61% for hen's egg and 27% for cow's milk.[7] These results indicate that therapeutic outcomes for wheat OIT seem to be better than those for cow's milk in patients with anaphylaxis. In spite of the original severity during DBPCFC, the adverse reaction rate was approximately only 10% in this study. However, there were 3 instances that required intramuscular adrenaline, as well as similar findings in other reports.[2,3] Therefore, this treatment should only be performed in a facility that specializes in food allergies and the management of anaphylaxis. Rescue treatment[6] for severe adverse reactions during OIT must be provided.

One of the limitations of this study is that subjects in the historical control group were not able to confirm their symptoms from OFC in the baseline. In addition, in the historical control group, there were only 7 subjects for whom wheat-sIgE could be evaluated over time. Further study is needed.

OIT for wheat-induced anaphylaxis increased the threshold dose of symptoms, achieved desensitization, and achieved tolerance in approximately 60% of the subjects in 2 years. In spite of the original severity identified by DBPCFC, wheat OIT using boiled udon seems safe, especially when compared with OIT using raw milk, which has a high incidence of adverse effects. OIT can be considered a useful form of therapy for the treatment of patients with wheat-induced anaphylaxis.

During the final preparation of this manuscript, Dr Tomohiro Utsunomiya passed away at the age of 38 years. We express our heartfelt condolences to his family. We are grateful to all our colleagues at Sagamihara National Hospital with whom we have worked since 2008.

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METHODS

DBPCFCs

The OFC was conducted via DBPCFC on admission. The subjects were informed that oral antihistamines and the oral steroid 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 created by heating at 1000 W for 90 seconds. The test was performed after confirming that the subjects were not allergic to either pumpkin or white sorghum.

The target of the trial food was a total amount of 1.3 g of wheat protein; subjects ingested the trial food every 15 minutes. The OFC was discontinued when objective symptoms (generalized urticaria, continuous coughing, moderate abdominal pain, vomiting, and diarrhea) that were moderate or severe developed. If mild subjective symptoms (pruritus of the throat or oral cavity, mild abdominal pain) or mild objective symptoms (localized urticaria or intermittent coughing) appeared during the OFC, the subject was 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, and at home, parents weighed the boiled udon noodles cooked at home using a scale.

Rush phase. Rush-phase OIT was conducted under careful observation by doctors during a 5-day admission of the subject (see Fig E1). Three days before admission, subjects were given oral antihistamines (loratadine) and leukotriene receptor antagonists (montelukast)[E1] 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 2 times a day and was stepped up or down on the basis of the severity of the adverse reaction (see Table E1).

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 phase was 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 the subject reached the target dose and did not develop any symptoms, orally administered loratadine and montelukast were discontinued. Then, the subject was allowed 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 subjects and their legal guardians on the treatment methods to use when symptoms developed. All subjects were prescribed antihistamines, oral steroids, inhaled β2 agonists, and adrenaline autoinjectors (Epipen). The emergency medicine systems included phones that were answered 24 hours a day by staff from our hospital. Subjects who lived far from the hospital were referred to and examined at an appropriate emergency location in advance.

Statistical analysis

For the patient profile, age and level of wheat-sIgE were determined and represented using median values. The Wilcoxon signed rank test was used to test the continuous variables between the 2 groups. The percentage of tolerant subjects at the end of the follow-up in each group was compared using Fisher exact test. In both cases, $P < .05$ was considered significant. GraphPad Prism (version 5, GraphPad Software, Inc, La Jolla, Calif) was used to perform the statistical analysis.

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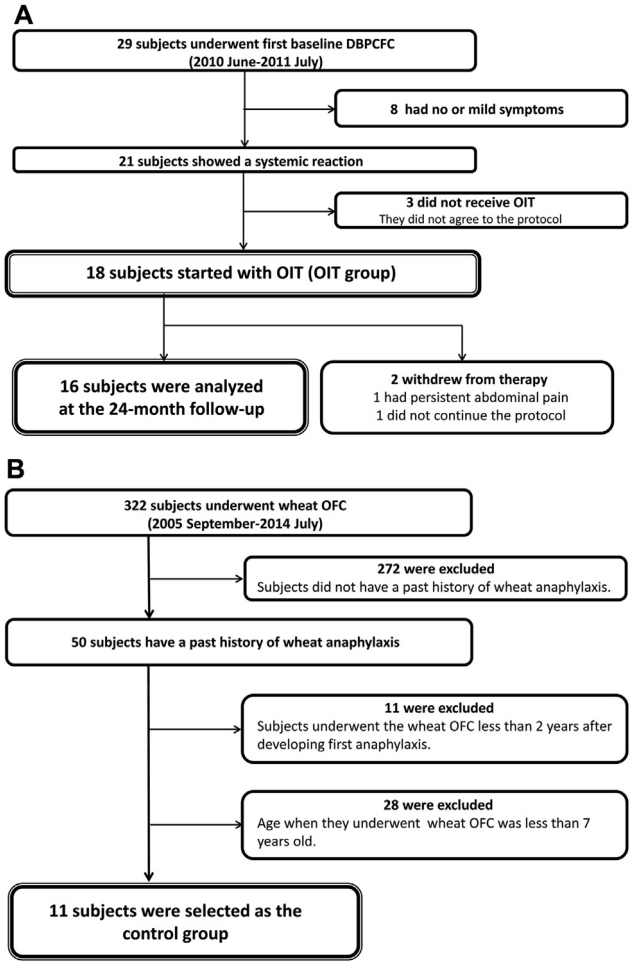

FIG E1. **A** and **B,** Flow diagram of this study.

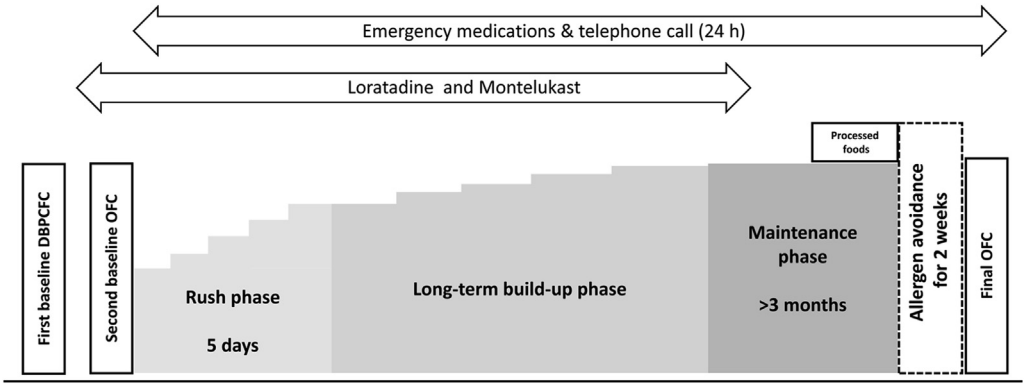

FIG E2. Study protocol. Our OIT protocol has 4 phases. The rush phase was performed in the hospital, and the long-term build-up and maintenance phase was then continued at home. Finally, the final OFC was performed to confirm acquisition tolerance after a 2-week complete avoidance of wheat.

TABLE E1. Baseline patients' profiles

Characteristic	OIT	Historical control
Subjects, n	18	11
Sex: male:female	11:7	9:2
Age (y), median (range)	9.0 (5.9-13.6)	7.0 (5.2-9.4)
Age at initial onset of wheat anaphylaxis (y), median (range)	—	3.0 (0.8-7.3)
Wheat-sIgE, median (range) (kU/L)	>100 (2.92->100)	>100 (2.5-100)
Symptom threshold doses at baseline DBPCFC, median (range) (g)	0.08 (0.02-1.3)	—

TABLE E2. Dosing schedule of OIT

Rush phase		Long-term build-up phase			
Step	Wheat protein (g)	Step	Wheat protein (g)	Step	Wheat protein (g)
1	0.05	1	0.26	11	2.86
2	0.10	2	0.52	12	3.12
3	0.21	3	0.78	13	3.38
4	0.42	4	1.04	14	3.64
5	0.78	5	1.3	15	3.9
6	1.3	6	1.56	16	4.16
7	1.82	7	1.82	17	4.42
8	2.6	8	2.08	18	4.68
9	3.9	9	2.34	19	4.94
10	5.2	10	2.6	20	5.2

TABLE E3. Severity grading of adverse reactions

	Grade		
Adverse reaction	**Mild**	**Moderate**	**Severe**
Skin			
Urticaria, pruritus, wheals	Localized or partial	Generalized	—
Itching	Weak	Strong	—
Mucosal tissue			
Eyelid or lip swelling	Swollen eyelids or lips	Whole face swollen	—
Sensation of discomfort	Pruritus of the throat or oral cavity	Throat pain	Tightness of throat, difficulty swallowing, hoarseness
Gastrointestinal tract			
Abdominal pain	Mild	Moderate	Abdominal cramps
Emesis, diarrhea	Nausea, emesis, diarrhea	Recurrent	Continuous loss of bowel control
Respiratory tract			
Cough, nasal congestion, sneezing, rhinorrhea	Intermittent cough, nasal congestion, sneezing, rhinorrhea	Repetitive cough	"Barky" cough, persistent cough
Wheeze, dyspnea	—	Chest tightness, mild wheezing	Apparent wheezing, dyspnea, cyanosis, saturation <92%, respiratory arrest
Cardiovascular			
Hypotension, change in heart rate	—	Facial pallor, mild hypotension, tachycardia (increase >15 beats/min)	Hypotension, dysrhythmia, severe bradycardia, cardiac arrest
Neurological			
Change in activity level, loss of consciousness	Change in activity level, tiredness	Feeling of "pending doom," light-headedness, somnolence	Confusion, loss of consciousness, incontinence

The severity grading of symptoms was investigated and assigned 3 grades, which was modified by the European Academy of Allergy and Clinical Immunology Taskforce. *Hypotension* was defined as systolic blood pressure with the following values: 1 mo to 1 y $<$ 70 mmHg; 1-10 y $<$(70 mmHg + [2 $\times$ age]); 11-17 y $<$ 90 mmHg. *Mild hypotension* was defined as systolic blood pressure with the following values: 1 mo to 1 y $<$ 80 mmHg; 1-10 y $<$(80 mmHg + [2 $\times$ age]); 11-17 y $<$ 100 mmHg.

TABLE E4. Adverse allergic reactions and their treatment during the OIT protocol

Adverse reactions and treatments	Rush phase (n = 18)	Long-term build-up and maintenance phase (n = 16)
Total number of intakes of OIT	143	5778
Adverse reactions, total, n (%)	42 (26.4)	486 (6.8)
Severity of symptoms, n (%)		
Mild	30 (18.9)	358 (5.0)
Moderate	12 (7.5)	125 (1.7)
Severe	0 (0)	3 (0.04)
Organ-specific symptoms, n (%)		
Skin	13 (8.2)	207 (2.9)
Mucosal	16 (10.1)	78 (1.1)
Gastrointestinal tract	20 (12.6)	162 (2.3)
Respiratory	22 (13.8)	234 (3.3)
Cardiovascular	0 (0)	1 (0.01)
Treatments, n (%)		
Total	16 (11.1)	186 (2.6)
Use of antihistamine oral or IV	11 (6.9)	141 (2.0)
Use of steroid oral or IV	0 (0)	42 (0.6)
Use of β2-inhalation	9 (5.7)	118 (1.7)
Use of adrenaline IM	0 (0)	3 (0.04)

IM, Intramuscular; *IV*, intravenous.