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

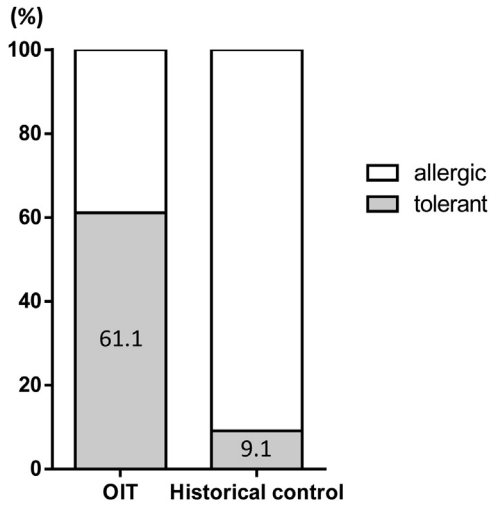

FIG 1. Comparison of outcome between OIT and control group in 2 years. The tolerance rate of the OIT group and the control group was determined as follows: tolerant (subject passed the final OFC), allergic (subject did not pass the final OFC in the OIT group or had an allergic reaction at the OFC or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

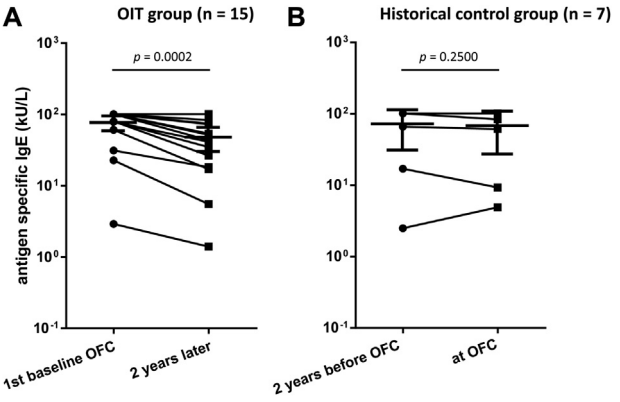

FIG 2. Changes in wheat-specific IgE level. Wheat-specific IgE level was measured using an immunoCAP instrument in the OIT group (n = 15) and the historical control group (n = 7). *P* value for the comparison between groups was calculated by using the Wilcoxon signed rank test.

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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