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Home-based up-dosing of wheat oral immunotherapy: Real-world effectiveness and predictive factor analysis

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Abstract

Background: Wheat allergy is one of the most prevalent allergens in Korea, decreasing quality of life and causing nutritional problems.

Objective: We aimed to investigate the efficacy and safety of the home-based wheat oral immunotherapy (OIT) using wheat noodles in children with a wheat allergy.

Methods: We conducted a retrospective study involving 72 children aged 3 to 17 years diagnosed with a wheat allergy. Patients received wheat OIT using boiled wheat noodles (n = 50) and were compared with a historical control group (n = 22). Baseline characteristics, adverse events, and immunological changes were assessed. Predictors of successful desensitization were identified using logistic regression analysis.

Results: Among 50 patients completing the up-dosing phase, 82.0% achieved desensitization to 2,400 mg of wheat protein, compared to 4.5% in the control group ($p < 0.001$). During the up-dosing period, the median number of adverse reactions per person was 2, and anaphylaxis occurred in 30.0% (15/50). However, there were no life-threatening adverse events. In multivariable analysis, the presence of asthma (adjusted odds ratio [aOR], 8.88; 95% confidence interval [CI], 1.10-71.97; $p = 0.041$) and a higher ratio of specific IgE (sIgE) to ω-5-gliadin and total IgE (aOR 19.09, 95%CI 1.21-300.80, $p = 0.036$) were significantly associated with treatment outcomes of wheat OIT.

Conclusion: Our study showed the safety and efficacy of home-based wheat OIT using boiled noodles in Korean children with wheat allergies. Careful consideration is warranted for patients with elevated baseline sIgE to ω-5-gliadin to total IgE ratio and a history of asthma.

Key words: Asthma, food allergy, ω-5-gliadin, oral immunotherapy, wheat allergy

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Introduction

Wheat is one of the most prevalent food allergens in the Korean population, contributing to a substantial 8-19% of cases with food-induced anaphylaxis.[1,2] Wheat allergies can occur both by ingestion or by inhalation, with a marked association with exercise-induced anaphylaxis.[3-5] Comparable to the challenges possessed by egg and milk allergies, patients with wheat allergy experience a notably decreased quality of life.[6,7] This reduction stems from the ubiquitous presence of wheat in processed foods, ranging from staple items such as bread, noodles, and rice cakes, to condiments like soy sauce.[8] Therefore, it is challenging to comprehensively restrict their consumption, which can also have nutritional problems.[6,7]

Oral immunotherapy (OIT) has been implemented worldwide to actively manage food allergies (FAs) and mitigate the risks associated with accidental exposure of offending foods.[9-12] Since 2022, OIT using heated milk or eggs has been evaluated by the New Health Technology Assessment system and employed for treating egg or milk allergies in Korea. However, despite the recent advancement of East Asia-centered studies, the efficacy and safety of wheat-OIT have not been determined in Korea.[13] Therefore, we aimed to provide real-world evidence regarding the usefulness and safety of OIT using home-based up-dosing protocol in Korean children with wheat allergies. Additionally, we conducted an analysis of clinical factors to predict favorable treatment outcomes.

Methods

Study Population

This study enrolled patients aged 3-17 years diagnosed with wheat allergy from October 2015 to July 2022. Diagnosis of wheat allergies was based on a positive oral food challenge (OFC) and a positive serum specific immunoglobulin (Ig) E level (≥ 0.35 kU/L) to wheat. Exclusion criteria included patients who had been on systemic corticosteroids, immunosuppressants, or biologics for a duration of more than four weeks prior to initiating OIT. Low adherence was defined as compliance below 80% in any aspect, including medication intake, hospital visits, or adherence to intake of food allergens during OIT. Patients lost to follow-up or with low adherence during the up-dosing phase were excluded due to indeterminate primary outcomes. Clinical and demographic data of the patients, including past medical history, symptoms after food exposure, and symptoms during OIT, were collected. For the historical control group, we meticulously selected patients diagnosed with wheat allergies who closely matched the age, levels of specific IgE (sIgE) to wheat, and intervals between sIgE tests of the OIT group. Additionally, the control group was identified from patients who had previously undergone diagnostic testing for wheat allergies using electronic medical records. These patients exhibited similar clinical presentations and met diagnostic criteria for wheat allergy as those in the OIT group. This study was approved by the institutional review boards of Samsung Medical Center (SMC-2020-06-124 and SMC-2021-04-115).

OFC and OIT Protocol and Desensitization

The OFC using plain boiled noodles was performed for all patients at the hospital within 3 months prior to initiating OIT. During the baseline OFC, incremental doses of wheat protein ranging from 0.3 mg to 3 mg, 15 mg, 30 mg, and 90 mg were administered at 20-minute intervals. The challenge was discontinued in the event of an allergic reaction, and the dose triggering these reactions was considered the eliciting dose. Subsequently, the initial daily home consumption for OIT was set at half the eliciting dose. Noodles were added to boiling water and cooked for 5 minutes, with noodle measurements for consumption conducted using an electronic scale accurate to two decimal places.

The OIT protocol consisted of an up-dosing phase and a maintenance phase (**Figure 1**). In the up-dosing phase, the dosage of boiled noodles was increased by 10 mg per week (equivalent to 0.3 mg of wheat protein) until reaching 100 mg (equivalent to 3 mg of wheat protein). Additional increments were made by 100 mg of boiled noodles every 3 to 7 days until reaching 3 g (equivalent to 90 mg of wheat protein). The doses were then further increased by

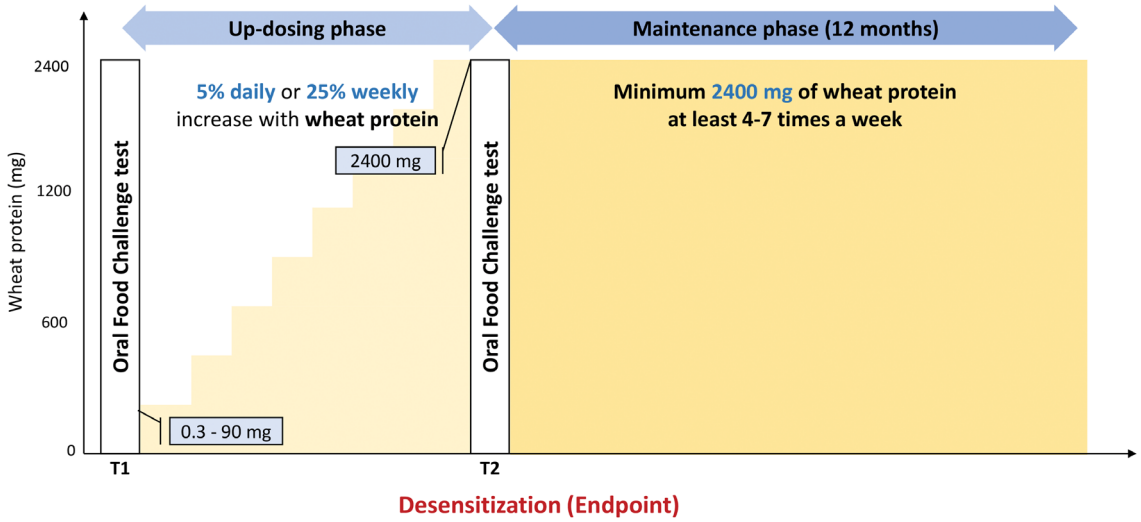

Figure 1. Protocol of wheat oral immunotherapy.

5% daily or by 25% weekly, reaching a target of 2,400 mg of wheat protein consumed at home. Once the dose exceeded 2,400 mg of wheat protein, patients were encouraged to continue consumption of at least 2,400 mg of wheat protein 4-7 times a week for a minimum of 12 months (maintenance dose).

Before starting OIT, detailed instructions were given to guardians regarding symptom management and the proper use of epinephrine auto-injectors in the case of anaphylaxis. Participants were asked to complete symptom diaries daily, using a call-based reporting system for severe reactions or frequent mild reactions. During the OIT process, clinician and registered nurses actively intervened, with monthly calls during the up-dosing phase and quarterly calls during the maintenance phase. If mild symptoms occurred during OIT, the same dose was maintained until next day. For moderate or severe symptoms, the dose was reduced to the previous dose and increased again when there were no symptoms. Participants were instructed not to exercise for 2 hours following a dose, and additional visits were performed if frequent or severe symptoms occurred. The severity of symptoms was assessed using the CoFAR grading system for allergic reactions.[14] Diagnosis of anaphylaxis was based on the guideline from the European Academy of Allergy and Clinical Immunology.[15,16] Desensitization was defined as no reactions during the OFC with an intake of a cumulative dose of 2,400 mg wheat protein after the up-dosing phase.

Data Collection

We collected clinical evaluations and laboratory test results at the following time points: at start of OIT (T1), and completion of the up-dosing phase (T2). Eosinophil counts in the peripheral blood, total IgE, wheat-sIgE, ω-5 gliadin-sIgE, wheat-specific immunoglobulin G4 (sIgG4), and ω-5 gliadin-sIgG4 levels were determined by immunoCAP (Thermo Fisher Scientific, Waltham, MA, USA). The cutoff value of sIgE for sensitization was 0.35 kU/L.

Statistical Analysis

Data were presented as numbers with percentages and medians with interquartile ranges (IQR). Fisher's exact test and the Kruskal-Wallis test were used to identify differences in baseline characteristics, differences in desensitization rate, adverse reactions, laboratory data, and follow-up duration between two groups. The Wilcoxon signed rank test was performed for the comparison of laboratory data between time points T1 and T2 within the same group. For analyses, concentrations of total IgE greater than 5,000 kU/L, sIgE greater than 100 kU/L and sIgG4 greater than 30 mg/L and less than 0.07 mg/L were assigned as 5,001 kU/L, 101 kU/L, 30 mg/L and 0.07 mg/L, respectively. In patients who completed the up-dosing phase, univariable and multivariable logistic regression analyses were used to assess associations between potential predictive factors and desensitization failure. Covariates with a $p < 0.1$ in the univariable analyses were chosen for inclusion in the multivariable analysis. Data were analyzed using SPSS for Windows (version 27.0, SPSS, Chicago, USA) and Graphpad Prism (version 9.0, Graphpad Software, San Diego, CA, USA). A P value less than 0.05 was considered statistically significant.

Results

Study population

Out of 70 patients who underwent wheat OIT, 20 were excluded because they were lost to follow-up (12/20) and low adherence to OIT protocol (8/20). The historical control group comprised 22 patients who continued with wheat restrictions and were matched based on age and wheat-sIgE levels with the OIT group. The participants had a median age of 5 years (4-6). No differences in baseline characteristics were found between the OIT and control groups (**Table 1**).

Table 1. Clinical characteristics of study participants.

	Total (N = 72)	OIT (n = 50)	Control (n = 22)	*p* value
Male	55 (76.4)	37 (74.0)	18 (81.8)	0.472
Age, years	5 (4–6)	5 (4–6)	4 (3–6)	0.121
Comorbidity				
Atopic dermatitis	45 (62.5)	30 (60.0)	15 (68.2)	0.509
Multiple food allergies	70 (97.2)	48 (96.0)	22 (100.0)	0.341
Asthma	22 (30.6)	16 (32.0)	6 (27.3)	0.688
Allergic rhinitis	35 (48.6)	22 (44.0)	13 (59.1)	0.238
Family history of allergic diseases*				
Atopic dermatitis	6 (8.3)	5 (10.0)	1 (4.5)	0.500
Food allergy	5 (6.9)	4 (8.0)	1 (4.5)	0.660
Asthma	3 (4.2)	3 (6.0)	0 (0.0)	0.263
Allergic rhinitis	9 (12.5)	6 (12.0)	3 (13.6)	0.735

Table 1. (Continued)

	Total (N = 72)	OIT (n = 50)	Control (n = 22)	*p* value
Experience of wheat allergy-related anaphylaxis	37 (51.4)	22 (44.0)	15 (68.2)	0.374
Total IgE (kU/L)	963.0 (318–1731.0)	997.5 (255.0–1984.0)	608.0 (404.0–1290.0)	0.611
Eosinophil count (/mm^3)	455.2 (299.9–621.2)	471.6 (329.3–586.8)	431.4 (260.1–690.9)	0.981
Specific IgE to wheat (kU/L)	49.2 (21.6–101.0)	51.2 (24.4–101.0)	47.4 (15.5–101.0)	0.723
Specific IgE to ω-5-gliadin (kU/L)	1.8 (0.6–9.2)	1.7 (0.6–8.1)	2.5 (0.7–12.7)	0.428

Continuous variables are presented as median (interquartile range) and categorical variables are presented as number (percent).
*Information on the family history of allergic diseases was missing for 2 subjects in the control group.
Abbreviations: OIT, oral immunotherapy

Desensitization and adverse reactions

A total of 50 children completed the up-dosing phase, with the median duration of 9 (7-10) months. Desensitization rate was 82.0% (41/50) in the OIT group, while 4.5% (1/22) of patients in the historical control group achieved desensitization. The proportion of desensitization in the OIT group was significantly higher than that in the control group ($p < 0.001$) (**Figure 2**).

During the up-dosing phase, the median number of adverse reactions per person was 2 (1-5). In the OIT group, 30.0% (15/50) exhibited at least one episode of anaphylaxis (**Table 2**). Of these allergic reactions, mild (CoFAR grade 1), moderate (CoFAR grade 2) and severe (CoFAR grade 3) reactions accounted for 40%, 16% and 22%, respectively.

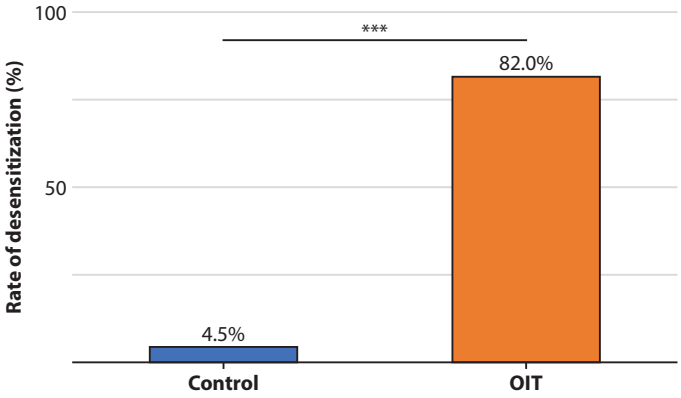

Figure 2. Desensitization rate of study participants.
***$p < 0.001$

Table 2. Adverse reactions during up-dosing phase in OIT group.

	Total (N = 50)	OIT-D* (n = 22)	OIT-W* (n = 28)	*p* value
Number of patients who experience of adverse reaction	39 (78.0)	16 (72.7)	23 (82.1)	0.425
Number of adverse reactions per patient	2 (1–5)	2 (0–6)	2 (1–4.5)	0.546
Experience of anaphylaxis	15 (30.0)	7 (31.8)	8 (28.6)	0.804
Severity of allergic reaction†				
Mild (CoFAR grade 1)	20 (40.0)	9 (40.9)	11 (39.3)	0.605
Moderate (CoFAR grade 2)	8 (16.0)	4 (18.2)	4 (14.3)	0.563
Severe (CoFAR grade 3)	11 (22.0)	3 (13.6)	8 (28.6)	0.274
Symptom type of allergic reaction				
Mucosa & skin	34 (68.0)	15 (68.2)	19 (67.9)	0.464
Respiratory	22 (44.0)	8 (36.3)	14 (50.0)	0.401
Gastrointestinal	7 (14.0)	5 (22.7)	2 (7.1)	0.082
Cardiac	0 (0.0)	0 (0.0)	0 (0.0)	-

Continuous variables are presented as median (interquartile range) and categorical variables are presented as number (percent).
*Doses were increased by 5% of the protein on a daily basis (OIT-D) or with 25% increments on a weekly basis (OIT-W) during up-dosing phase.
†Symptom severity was scored by CoFAR Grading Scale for Systemic Allergic Reactions. With scores ranging from 1 (transient or mild discomfort) to 5 (death); there was no reports of grade 4 (life-threatening) or grade 5 (death). The data present the maximum severity among patients who experienced adverse reactions.
Abbreviations: OIT, oral immunotherapy

There were no reports of life-threatening allergic reactions (≥ CoFAR grade 4). The most prevalent adverse reactions manifested as mucosal and skin symptoms (68%), followed by respiratory symptoms (44%) and gastrointestinal symptoms (14%). In the maintenance phase, 15 (30%) patients in the OIT group experienced adverse reactions. Most of them were mild (CoFAR grade 1) but three patients had moderate (CoFAR grade 2) reactions. There were no severe (≥ CoFAR grade 3) reactions.

Clinical course after assessment of desensitization

The total median duration of follow-up from T1 for the study population was 31.5 (27-44) months. No significant difference in the duration of follow-up was observed between the OIT and control groups (p = 0.186). At the latest follow-up assessment, 88% (44/50) of the OIT group who completed the up-dosing phase showed unrestricted consumption of various forms of wheat-containing foods, even including the three patients who did not pass the 2,400 mg of OFC at the end of the up-dosing phase. Four other patients continued with wheat restrictions due to not achieving successful desensitization. One patient could only consume small quantities of wheat, and allergic reactions occurred during exercise. Another patient was successfully maintaining a low-dose intake (150 mg of wheat protein) without experiencing any allergic reactions. However, in the control group, only two (9.1%) children could tolerate wheat consumption without OIT, while 20 (90.9%) children chose to restrict their wheat intake. Of these patients, 10 (45.5%) children showed allergic reactions to wheat OFC or and 10 (45.5%) children continued to avoid wheat without undergoing OFC due to concerns of potential allergic reactions.

Immunologic profiles

In the OIT group, wheat-sIgE and ω-5 gliadin-sIgE levels in the OIT group showed significant reductions between T1 and T2 (both p < 0.001) (**Figure 3A and 3B**). The changes in wheat-sIgE (median difference, -6.34 kU/L; 95%CI, -14.89 to 0 kU/L) and ω-5 gliadin-sIgE (median difference, -0.90 kU/L; 95%CI, -1.51 to -0.47 kU/L) in the OIT group were significantly higher than those in the control group (both median difference, 0 kU/L; 95%CI -1.17 to 1.54 kU/L in wheat-sIgE and -0.72 to 0.83 kU/L in ω-5 gliadin-sIgE) (p = 0.005 and 0.001, respectively).

The sIgG4 to wheat in OIT group significantly increased (p = 0.024), whereas the control group did not show a significant change (p = 0.483) (**Figure 3C**). There were no significant changes in sIgG4 levels to ω-5 gliadin in either group (p = 0.609 in OIT group and 0.750 in control group, respectively) (**Figure 3D**). The ratios of sIgG4/sIgE to wheat and ω-5 gliadin significantly increased in the OIT group (both p < 0.001) (**Figure 3E and 3F**). In addition, the levels of eosinophil count decreased during OIT (p = 0.041), while no changes in eosinophil count were found between T1 and T2 in the control group (p = 0.811). While the levels of total IgE significantly increased in the control group (p = 0.048), no change was noted in the OIT group (p = 0.644).

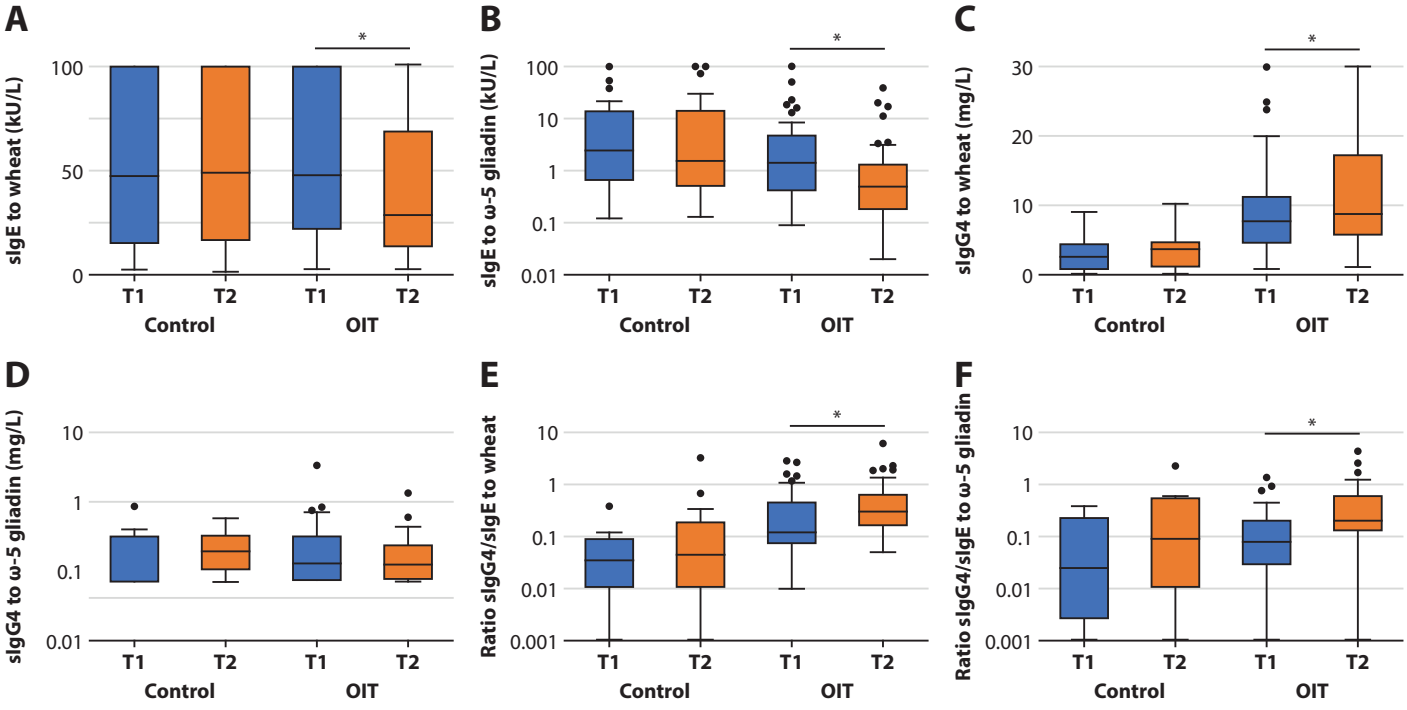

Figure 3. Immunological changes between before (T1) and after (T2) of oral immunotherapy. (A) Specific IgE (sIgE) to wheat, (B) sIgE to ω-5-gliadin, (C) specific IgG4 (sIgG4) to wheat, (D) sIgG4 to ω-5-gliadin, (E) sIgG4/sIgE ratio to wheat, and (F) sIgG4/sIgE ratio to ω-5-gliadin.

*p < 0.05

Table 3. Risk factors influencing desensitization failure in the OIT group.

	Number	Univariable analysis			Multivariable analysis		
		OR	95%CI	*P* value	aOR	95%CI	*P* value
Sex (male)	37/50	3.31	0.37-29.43	0.283			
Age ≥ 6 yr	19/50	1.15	0.25-5.30	0.854			
Atopic dermatitis	30/50	0.46	0.11-2.00	0.299			
Allergic rhinitis	22/50	1.02	0.24-4.37	0.976			
Asthma	16/50	6.20	1.31-29.46	0.022	8.88	1.10-71.97	0.041
Anaphylaxis at baseline OFC	27/50	9.26	1.06-80.93	0.044	3.35	0.21-53.01	0.391
Eosinophil ≥ 500 /mm^3	22/50	1.00	0.24-4.37	0.976			
sIgG4/IgE to wheat at T1 < median	19/38	3.04	0.51-18.11	0.223			
sIgG4/IgE to gliadin at T1 < median	17/38	3.96	0.66-23.76	0.132			
wheat-sIgE/total IgE at T1 ≥ median	25/48	4.08	0.75-22.19	0.103			
ω-5-gliadin-sIgE/total IgE at T1 ≥ median	17/48	26.67	2.93-242.67	0.004	19.09	1.21-300.80	0.036
Increment in eosinophil between T1 and T2	19/50	0.40	0.07-2.19	0.292			
Increment in total IgE between T1 and T2	27/48	1.72	0.37-7.86	0.488			
Increment in wheat-sIgE between T1 and T2	19/50	2.41	0.56-10.43	0.239			
Increment in ω-5-gliadin-sIgE between T1 and T2	5/49	3.52	0.50-25.10	0.209			
Decrement in sIgG4 to wheat between T1 and T2	11/38	0.98	0.16-6.00	0.981			
Decrement in sIgG4 to ω-5-gliadin between T1 and T2	17/36	0.80	0.15-4.25	0.797			
Anaphylaxis ≥ 2 episodes during up-dosing phase	12/50	6.07	1.29-28.49	0.022	1.07	0.12-9.20	0.952

Abbreviations: OIT, oral immunotherapy; OFC, oral food challenge; OR, odds ratio; aOR, adjusted odds ratio

Predictive factors influencing desensitization in the OIT group

Univariable and multivariable logistic regression analyses were performed to identify risk factors for desensitization failure in patients who completed the up-dosing phase (**Table 3**). Univariable logistic regression analysis showed that the presence of anaphylaxis at the baseline OFC, a history of asthma, a higher ratio (≥ 0.01) of sIgE to ω-5-gliadin to total IgE at T1, and experience of anaphylaxis ≥ 2 episodes during the up-dosing phase were significantly associated with treatment outcomes in the OIT group (p = 0.044, 0.022, 0.004, and 0.022 respectively). In the multivariable analysis, the presence of asthma (aOR 8.88, 95%CI 1.10-71.97, p = 0.041) and a higher ratio (≥ 0.01) of sIgE to ω-5-gliadin to total IgE at T1 (aOR 19.09, 95%CI 1.21-300.80, p = 0.036) were significantly associated with failure of desensitization after wheat OIT.

Discussion

To the best of our knowledge, this study represents the first investigation into the efficacy and safety of wheat OIT in Korean children. Unlike the extensively studied immunotherapies for milk, egg, and peanut allergies,[17-21] wheat OIT has received relatively less research attention. Our findings demonstrated the effectiveness of a home-based up-dosing wheat OIT using boiled noodles, achieving desensitization to 2,400 mg protein in 82.0% of children in the OIT group compared to only 4.5% in the control group. Although children in the OIT group experienced a median of two adverse reactions per person, with 30% encountering anaphylaxis at least once, no severe allergic reactions occurred during the home-based up-dosing period. In comparison to the control group, wheat OIT induced significant changes in immune parameters including specific IgE levels to wheat, ω-5-gliadin, as well as specific IgG4 levels to wheat.

The desensitization dose in previous studies has ranged from 53 to 7,443 mg of wheat protein, with desensitization rates varying from 23% to 100%.[3,9,11,21-23] A multicenter, randomized, double-blinded, placebo-controlled trial showed that wheat OIT using wheat flour induced desensitization in about 52.2% (12/23) of low-dose wheat OIT group and 57.1% (12/21) of high-dose wheat OIT group after 1 year of treatment.[3] A prospective open-label multicenter study found that 64 out of 100 participants aged 6-18 years who underwent wheat OIT reached the target dose of 2,000 mg of wheat protein at the end of the 17-week build-up period.[22] While comparing desensitization rates is challenging due to variations in definitions and study populations, the desensitization rates observed at the end of the up-dosing phase in our present study tend to be higher compared to those in previous studies. This outcome can be attributed to several factors, including the severity of wheat allergy and the timing of desensitization assessment. Above all, the percentage of subjects who experienced wheat-induced anaphylaxis at baseline was relatively low at 44.0% in the current study, in contrast to findings in other studies.[9,11] Nevertheless, our wheat OIT protocol revealed the potential for successful desensitization in a home setting.

In this study, we observed an incidence of adverse events and anaphylaxis during the up-dosing phase of 78.0% and 30%, respectively. These rates are consistent with those reported in other studies, which have ranged from 33.3% to 100% for adverse events and from 16.6% to 33.3% for anaphylaxis.[3,21,23-27] However, there were no life-threatening reactions, including persistent hypotension or hypoxia (≥ COFAR grade 4). Makita et al. also found no fatal reactions during their rush OIT protocol.[24] However, a Finnish study showed wheat OIT was associated with 14% (14/100) severe adverse reactions during the up-dosing phase.[22] Babaie et al reported that 0.4% of severe reactions occurred during the up-dosing phase, with doses reaching up to 5,280 mg protein.[11] Despite the similarity in results across studies, there is still a need for improvement in the safety profiles of home-based OIT protocols for wheat allergy. Strategies to enhance safety may include the implementation of pre-medication strategies, the adoption of tailored management approaches based on risk stratification, and the provision of detailed instructions for participants and caregivers to effectively manage adverse reactions before starting OIT. Additionally, cofactors that could exacerbate allergic reactions, such as infections, exercise immediately after intake, and consumption on an empty stomach, should be thoroughly controlled. The procedures may contribute to the safety of home-based OIT for wheat observed in our home-based wheat OIT protocol.

We also noted a remarkable decrease in the sIgE levels to wheat and ω-5-gliadin after a median of 9 months of OIT. A Japanese study on OIT for wheat allergies showed that sIgE to wheat and ω-5-gliadin significantly decreased after 1-1.5 years of OIT.[21] However, an initial increase in sIgE levels during the build-up phase can be expected due to the expansion of allergen-specific Th2 cells.[28] A US study reported that the median levels of sIgE to wheat and ω-5-gliadin increased at 12 weeks compared to the baseline, but continued to decrease at 26 weeks and 52 weeks.[3] These findings indicate that sIgE levels to wheat might depend on duration and dose of OIT, and our wheat OIT protocol led to a decrease in wheat and ω-5-gliadin sIgE concentrations. Furthermore, our study showed no significant changes in immunological parameters in the control group, consistent with prior research.[27] Previous studies on wheat OIT study showed that sIgG4 levels against wheat and ω-5-gliadin were significantly increased after up-dosing phase.[3,26,27] In our present study, changes in sIgG4 levels to wheat were consistent with previous findings, but this was not the case for sIgG4 levels to ω-5-gliadin. This discrepancy may be attributable to the small numbers of patients (36/50) whose sIgG4 levels to ω-5-gliadin were measured at both T1 and T2, with a median value of only 0.14 kU/L at T1 and 0.16 kU/L at T2.

Although the efficacy and safety of OIT have been widely investigated, the predictors of clinical response are still unclear. Because previous studies on dosing protocols and primary end points for wheat OIT displayed significant heterogeneity, many of these studies involved small study populations, with participant numbers ranging from as few as six to a maximum of 100.[22,26] Therefore, only a limited number of studies have performed predictive factor analysis. A recent study in Taiwan on wheat OIT identified higher initial levels of specific IgE to wheat and ω-5-gliadin as risk factors for treatment difficulties.[29] This is the first study to reveal that the baseline ratio of sIgE to ω-5-gliadin to total IgE and asthma are independent risk factors for OIT failure. These results correspond with the results of previous studies, which reported that the serum sIgE/total IgE ratio was the best predictor of clinical response to allergen-specific immunotherapy in patients with allergic rhinitis.[30] A Japanese study for long-term follow-up of fixed low-dose wheat OIT showed that the baseline gluten- and ω-5-gliadin-sIgE in the short-term unresponsiveness group were significantly lower than those in the treatment failure group.[9] However, Sato et al reported no significant differences in wheat-sIgE between tolerant and allergic subjects in the OIT group.[23] Large-scale, multicenter studies that include a diverse range of patients with wheat allergies are warranted to establish reliable predictors of treatment success or failure.

Our current study has some limitations, primarily due to its retrospective design. Firstly, our investigation of OIT efficacy and safety during the up-dosing phase, which involved matching participants with a historical control group, led to the exclusion of participants who did not complete this phase. Secondly, the reliance on self-reported symptoms for severity of adverse reactions, despite follow-up interviews by trained clinical staff for more detailed information, introduces a level of uncertainty in the accuracy of the grading system used. Furthermore, caution is essential when interpreting our results, given that not all patients in the control group underwent an OFC. In addition, the study observed a high dropout rate of 28.6%, which may affect a significant portion of the sample size and potentially lead to an overestimation of desensitization rates. Despite these limitations, our findings are noteworthy, demonstrating that children with severe wheat allergies can successfully undergo home-based up-dosing OIT without severe adverse events, thereby achieving successful desensitization.

In conclusion, our study showed that a home-based up-dosing protocol using boiled noodles for wheat OIT can be safe and effective for desensitization in children with wheat allergies in real-world practice. Notably, our findings highlight the importance of caution when considering patients with a high baseline serum sIgE to ω-5-gliadin to total IgE ratio and a history of asthma, which were potential indicators of a higher likelihood of treatment failure.

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Conflicts of Interest

The authors have no relevant conflicts of interest.

Author's Contributions

- JihK, KA, JYL, and MK designed the study.
- JiwK, MJ, SJ, SS, JS, SK, HMK, YK, MHL, SJL, and JihK contributed to data collection.
- YK and MHL curated data.
- JiwK, MJ, SK, and JihK performed the statistical analysis and interpretation of the results.
- JiwK, MJ, MK, and JihK prepared draft manuscript.
- JihK and MK performed project administration.
- All authors reviewed the results and approved the final version of the manuscript.

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