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A Safe and Effective Method for Wheat Oral Immunotherapy

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ABSTRACT

At present the only available management for food allergy is avoidance; however, abstaining from allergic foods can affect the quality of life. Oral Immunotherapy (OIT) is an efficient method for increasing tolerance towards food allergens.

The aim of this study was desensitizing patients above five years of age with wheat allergy and evaluating the safety and efficacy of OIT for children with IgE-mediated wheat allergy.

The method of Rush Oral Immunotherapy (ROIT) was performed on 8 anaphylactic wheat allergic patients as well as outpatient method on 5 non-anaphylactic ones. In ROIT, build-up phase was performed during several days, but in outpatient, the amount of ingestion gradually increased to 5.2 g wheat protein within several weeks. After that, maintenance doses were prescribed daily for 3 months. Then, if the oral food challenge (OFC) was negative, the patients were considered to be in desensitized state, which meant they had to continue eating same doses without interruption.

In ROIT, build-up phase continued for about 4.6 days during which, 21 from 71 doses, showed clinical symptoms (29.6%). On the contrary, outpatient method lasted approximately 72.4 days in which 356 doses were used and symptoms developed in only 9 doses (2.5%). In total –regardless of type of build-up phase– 12 patients could complete the maintenance phase with 1080 doses that 28 of them (2.6%) developed mild symptoms.

Our OIT study proved to be safe and effective, although it is utterly evident that further investigation on more patients is necessary.

Keywords: Food allergy; Food hypersensitivity; Food immunotherapy; Oral desensitization; Wheat; Wheat hypersensitivity

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INTRODUCTION

Wheat is listed among the eight most common food allergens.[1] An estimate of prevalence of wheat allergy

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in general population is between 0 to 1.2%[2] but unfortunately there is not any precise estimation of wheat allergy in Iran. A study in Japan determined wheat allergy prevalence about 0.2 to 0.9% in adults and 0.4 to 1.3% amongst children.[3] Wheat and other cereals contain some proteins that are involved in causing allergic reactions. Globulin and glutenin are major allergens in posing IgE-dependent reactions; gliadin is the primary factor in celiac and food-dependant exercise-induced anaphylaxis.[4] Several salt-soluble proteins (albumins and globulins) play a pivotal role in causing Baker's asthma.[5] IgE-mediated food allergic reactions usually occur within minutes or hours after encountering with food allergen. Common complications range from skin symptoms, gastrointestinal disturbances and respiratory disorders to anaphylaxis.[6] Currently the only way to prevent these symptoms is avoiding food allergens together with medical treatment in cases of accidental ingestion and anaphylaxis. Moreover, it is very difficult to keep this diet for children [7]. Fortunately, treatment strategies have been explored[8] to solve these serious problems. Recently many researches have been conducted to evaluate the efficiency of oral immunotherapy (OIT) on food allergic patients;[9] however, just a few studies have focused on wheat OIT.[10-14] In the present study we followed the same protocol, but with a number of modifications, as Motohiro Ebisawa and colleagues who have been conducting studies[13,14] on wheat OIT at Sagamihara National Hospital in Japan. This interventional study aimed to evaluate the safety and efficacy of this protocol of OIT, in patients with IgE-mediated wheat allergy.

MATERIALS AND METHODS

Patient Selection

We selected 5-year-old patients or older, who had a history of allergy to wheat. A positive skin prick test response to wheat flour was indicated by wheals ≥3 mm larger than those created by the saline control. Wheat allergy in these patients was confirmed by using double blind placebo control food challenge (DBPCFC) and oral food challenge (OFC) test. Those who suffered from severe and uncontrolled asthma, chronic urticaria and significant systemic disease or had poor compliance were excluded from our study. The course of this study was explained to patients, their parents or caregivers and a written consent was obtained from all of them. They were also informed about the research confidentiality and the right of withdraw during the study. This study is approved by Iranian Registry of Clinical Trials (IRCT: 201204199510N1).

OIT Protocol

Patients were divided into two groups of anaphylactic and non-anaphylactic, according to their history and symptoms during DBPCFC and based on clinical criteria for anaphylaxis diagnosis.[15]. We performed ROIT on anaphylactic and outpatient method on non-anaphylactic wheat allergic patients. The research method consisted of initial build-up phase followed by a maintenance phase. Maximum dose during build-up phase was 5.2 g wheat protein, supplied in 52 g bread with 10% wheat protein. In ROIT, patients were hospitalized for a few days to perform build-up phase. In outpatient method this was performed within a few weeks at home. After completion of this phase, the participants were asked to ingest the maintenance dose daily for three months. Then, the OFC test by using 52 g bread was performed which determined whether they could be regarded to be in desensitized state or not. However, in this level, we were not confident about achieving tolerance. Therefore, we asked them to eat at least 5.2 g wheat protein every day.

DBPCFC

In DBPCFC, patients received 25 g of bread that consisted of a mixture of rice and corn flour as placebo or the same amount of bread containing 1.3 g of wheat protein without premedication in different days. The bread was divided into 16 pieces to be taken in time interval of 15 minutes and each time patients received some pieces as shown in Table 1. The challenge was considered positive, when moderate symptoms such as generalized urticaria or respiratory and gastrointestinal symptoms were shown. In such a case, we prescribed antihistamines, inhaled beta 2-agonist or systemic steroids.

Build-up Phase

ROIT

After DBPCFC and three days before admission, anaphylactic patients took 5 mg of loratadine and 5 mg of montelukast on a daily basis to prevent severe adverse reactions. The starting dose of wheat protein for each patient was calculated according to OFC with

Table 1. The amount and duration of bread ingestion in double blind placebo control food challenge in patients with wheat allergy

Time (min.)		0	15	30	45	60
Single dose	Bread	1/16*	1/16	1/8	¼	1/2
Cumulative dose	Bread	1/16	1/8	1/4	½	1
	Wheat protein	0.08 g	0.16 g	0.33 g	0.65 g	1.3 g

* portion of bread used in double blind placebo control food challenge

Table 2. Relationship between the results of oral food challenge (OFC) and the initial dose of rush oral immunotherapy (ROIT) in patients with wheat allergy

Time (min)			0	15	30	45	60
OFC	Single dose	Bread (1 unit)	1/16	1/16	1/8	¼	½
	Cumulative dose	Bread	1/16	1/8	1/4	½	1
		Protein (g)	0.08 g	0.16 g	0.33 g	0.65 g	1.3 g
	Level of threshold eliciting systemic reactions in OFC		2	3	4	5	6
Starting level of ROIT (in case severe reactions were elicited)			3(1)	4(2)	5(3)	6(4)	7(5)

premedication. On the first day of admission, the OFC test was conducted to achieve initial dose for ROIT. In OFC patients received a piece of bread containing 1.3 g of wheat protein. The bread was divided into 16 pieces to be taken in time interval of 15 minutes and each time patients received some pieces as shown in Table 2.

The cumulative dose which patients could take was regarded as the threshold. We categorized clinical symptoms as mild, moderate and severe reactions.[16] If adverse reactions in OFC were moderate the initial dose of ROIT was increased from threshold, whereas it was decreased in case of showing severe symptoms (Tables 2 and 3). In build-up phase, patients took bread two times a day (9 AM and 2 PM), and if they could take it without any reactions or with mild reactions or with moderate reactions for one time, they were asked to take bread with a 50% increase in the former dose. In cases of showing moderate symptoms for two times the amount of bread was not changed. When patients experienced any kinds of symptom more than two times, the amount of bread was reduced. Patients were discharged after finishing build-up phase and the maintenance phase continued at home.

Outpatient Method

Five patients underwent wheat OIT by outpatient method. After performing OFC without premedication, we calculated starting dose of wheat protein for them. In this method, after the threshold dose was determined in OFC, patients were asked to ingest a small amount of wheat daily at home which was started by taking 1/4 of the threshold dose. The amount of wheat ingestion was increased gradually to 52 g of bread (Table 4). If patients did not have any symptoms in three consecutive days, the amount of wheat ingestion was increased one level. This dose was not changed in case of showing mild symptoms in patients. In case of dealing with moderate reactions, the dose level was decreased one by one. Eventually, if the symptoms were so severe, participants had to discontinue eating bread and consult their doctor.

Table 3. The amount of wheat protein for starting oral immunotherapy (ROIT) in patients with wheat allergy

Level	1	2	3	4	5	6	7
Wheat protein(g)	0.05	0.10	0.21	0.42	0.78	1.3	1.82

Table 4. Amount of wheat ingestion in build-up phase in outpatient method of wheat allergy immunotherapy

LEVEL	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Wheat protein(g)	0.13	0.26	0.39	0.52	0.65	0.78	0.91	1.04	1.17	1.3
LEVEL	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**
Wheat protein(g)	1.56	1.82	2.08	2.34	2.6	2.86	3.12	3.38	3.64	3.9
LEVEL	**21**	**22**	**23**	**24**	**25**					
Wheat protein(g)	4.16	4.42	4.68	4.49	5.2					

Maintenance Phase

In both groups after completion of build-up phase, patients were asked to ingest 52 g of bread as maintenance dose on a daily basis for a period of 3 months. In the first month they had to continue wheat-elimination diet, but after that, they were permitted to eat the processed foods containing <0.65 g of wheat protein per day to improve their quality of life.

Follow up

The patients' parents or caregivers were requested to fill a daily form, including information about the time and amount of daily ingestion of bread, severity of complications that occurred after wheat ingestion and the use of prescribed medication for them. Parents were asked to observe their children at least for one hour after ingestion of bread. The participants were also asked to take rest after the ingestion. An action plan was provided for each patient and antihistamine, corticosteroid, β2-agonist inhalers and epinephrine auto-injector were prescribed to tackle adverse reactions.

Food Challenge

In both groups at the end of maintenance phase we performed OFC with 52 g of bread. If the patient could pass the test, we regarded them as being in desensitized state which meant they could ingest wheat products without any restrictions. Since we were not sure whether patients had got tolerance or not, those who completed treatment had to eat at least 5.2 g wheat protein every day. As they usually had the same amount of wheat products in their daily diet, it was no difficulty for most of them to eat this dose each day.

Wheat specific-IgE Concentrations and Skin Prick Test

The measurement of serum specific IgE to wheat using the ImmunoCAP100 system (Phadia, Uppsala, Sweden) and skin prick test using wheat flour extract (Greer company Code: F235, USA) were performed before OIT and after completion of maintenance phase. We used SPSS (version 11, SPSS, Inc, Chicago, IL, USA) pair T test for statistical analysis.

RESULTS

Subjects

During the study period, 24 patients above 5 years of age with the history of wheat allergy were referred to our clinic and DBPCFC and OFC tests were done for them to confirm their diagnosis. Wheat allergy was confirmed in 15 patients. According to clinical criteria for diagnosis of anaphylaxis, nine patients had anaphylaxis (7 boys- 2girls). In the anaphylactic group, one patient did not accept hospitalization for treatment and was excluded from the study and the 8 remaining patients underwent ROIT. In the non-anaphylactic group one patient with wheat-dependent exercise-induced food allergy was excluded and five patients underwent wheat OIT by using outpatient method. Table 5 represents demographics of 13 studied patients. The average age of patients at beginning of the study was 7 years old (min=5.5- max=19 years). Nine patients (69%) had asthma, 7 of whom were in anaphylactic group and 8 patients (62%) had other concomitant food allergies,5 of whom belonged to the anaphylactic group. The most common initial symptom after ingestion of wheat products was skin manifestations including urticaria, angoiedema, flushing, and pruritis. All 13 patients successfully completed the initial build-up phase. One other patient of the anaphylactic group discontinued the maintenance phase for personal reasons. 12 remaining patients completed maintenance phase; thus, they could ingest wheat product freely without any complications.

DBPCFC

The cumulative doses of wheat protein that induce skin, respiratory, and gastrointestinal symptoms

Table 5. Demographics of the patients with wheat allergy, results of double blind placebo control food challenge (DBPCFC) and oral food challenge (OFC), and starting dose of oral immunotherapy (OIT) for each patient

Subject ID (sex)		Age at study entry (year)	Atopic co-morbidity	Other food allergy	DBPCFC Threshold of reactivity Wheat protein(g)	OFC Threshold of reactivity Wheat protein(g)	Starting dose of OIT Wheat protein(g)
Anaphylactic group	01 (M)	5	Asthma	Egg, fish	0.33	1.3	0.78
	02 (M)	7	Asthma	Oat	0.33	1.3	0.78
	03 (M)	5.5	Asthma	Oat	1.3	1.3	0.78
	04 (M)	5	Asthma	-	0.16	0.16	0.1
	05 (F)	5.5	Asthma	-	0.16	0.16	0.1
	06 (M)	7	Asthma	-	0.64	0.64	0.42
	07 (F)	7	-	Oat	0.33	0.33	0.21
	08 (M)	5	Asthma	Oat	0.33	0.33	0.21
Non- anaphylactic group	09 (F)	5	Asthma	Soya	1.3<	2	0.5
	010 (F)	19	-	-	1.3<	5.2	1.3
	011 (M)	6	Asthma	-	1.3<	1.8	0.4
	012 (M)	5.5	-	Tree nut, kiwi	1.3<	5.2	1.3
	013 (M)	8	-	oat	pass	5.2	1.3

during DBPCFC and OFC as well as starting dose of OIT for each patient are shown in Table 8. In anaphylactic group, the mean wheat protein which triggered symptoms during DBPCFC was 0.45 g (range 0.16-1.3 g); however, this ratio was 3.1 g (range 1.3-5.2 g) in non-anaphylactic group during OFC. All subjects with positive result in OFC showed skin manifestation including flushing and urticaria. Five patients experienced upper respiratory symptoms such as sneezing and rhinorrhea, six subjects developed respiratory distress and wheezing, five other patients experienced abdominal pain and vomiting, and none of them had hypotension. In order to relieve the symptoms, all the patients received diphenhydramine, six patients were also treated with β2-agonist inhaler and for 5 other patients with severe symptoms epinephrine was prescribed.

Build-up Phase

Table 6 summarizes duration, number of doses, symptoms, and type of received treatment during this phase.

ROIT

Eight patients in anaphylactic group underwent ROIT. Average duration of ROIT was 4.6 days (range 3-6 days). All subjects could complete build-up phase successfully and tolerated 5.2 g wheat protein. During this phase, seven out of eight patients (87.5%) experienced skin, respiratory, and gastrointestinal symptoms requiring treatment (Table 6). In ROIT, during build-up phase a total number of 71 doses were applied. 21 of 71 applied doses (29.6%) developed mild symptoms, which meant those patients who followed this pattern needed treatment. The most common symptom was skin manifestation such

Table 6. Build-up phase of oral immunotherapy in patients with wheat allergy: duration, number of applied doses, symptoms and kind of treatment for each patient.

Subject ID		Duration of Build-up phase (days)	Number of doses in build-up phase	Number of doses that showed symptoms	Symptoms observed during build up phase	Treatment
Anaphylactic group	01	3	6	2	LU,V	Oral diphenhydramine
	02	3	6	1	LU,MRD	Oral diphenhydramine SABA
	03	3	6	0	-	-
	04	5	10	1	LU,C	Oral diphenhydramine SABA
	05	6	11	3	LU,C	Oral diphenhydramine SABA
	06	5	9	2	AP,C,F,GU	Oral diphenhydramine SABA- Epinephrine
	07	6	11	3	GU,SRD,W,C	Oral diphenhydramine SABA- Epinephrine
	08	6	12	9	V,GU,F	Oral diphenhydramine Epinephrine
Non-anaphylactic group	09	87	87	0	-	-
	010	66	66	0	-	-
	011	66	66	2	GU	Oral diphenhydramine
	012	82	82	9	LU,V,MRD	Oral diphenhydramine SABA
	013	55	55	0	-	-

LU: localized urticaria; MRD: mild respiratory distress; AP: abdominal pain; C: coughing; F: flushing; GU: generalized urticaria; SRD: severe respiratory distress; W: wheezing; V: vomiting; SABA: short-acting β agonists.

as urticaria and flushing that it occurred in 16 of doses (23%) for 7 patients. Respiratory symptoms including sneezing, coughing and wheezing were seen in 6 doses (8.7%) in 5 subjects. Gastrointestinal symptoms including vomiting and abdominal pain occurred in 3 of patients in 4 doses (5.7%). Oral diphenhydramine was the most common drug used in 17 of 71 doses (23.9%) in order to treat patients. Short acting β 2 agonist inhaler was prescribed for five patients in 5 of 71 doses (7.2%). Three patients (37/5%) developed severe symptoms such as generalized urticaria and respiratory distress, which was controlled with epinephrine. The number of prescribed epinephrines was 4 in total 71 applied doses (5.6%).

Outpatient Method

The mean duration of build-up phase in this method was 72.4 days (range 66-87 days). All patients could increase the doses to 5.2 g wheat protein based on the outpatient protocol. The total number of applied doses was 356, in 9 of which some mild reactions were observed (2.5%).

Maintenance Phase

Twelve of 13 studied patients completed maintenance phase. The total number of applied doses in maintenance phase was 1080, in 28 (only 2.6% of doses) of which symptoms occurred only amongst anaphylactic patients. The subject No. 06 showed mild symptoms including abdominal pain, urticaria and wheezing in 14 applied doses in the first month of maintenance phase and was treated with oral diphenhydramine and inhalation of β2 agonists. Subject No. 07 in the second week of maintenance phase experienced local urticaria in 3 doses, for control of which oral diphenhydramine was prescribed (Table 7).

Skin Prick Test and Wheat Specific IgE Level

Baseline mean of wheal diameter of skin prick test for wheat flour extract in anaphylactic and non-anaphylactic group was 9 mm (min=8, max=10mm)

Table7. Maintenance phase of oral immunotherapy in patients with wheat allergy: duration, number of applied doses, symptoms and kind of treatment for each patient.

Subject ID		Duration of maintenance phase (days)	Number of doses in maintenance phase	Number of doses with symptoms	Symptoms observed during maintenance phase	Treatment
Anaphylactic	01	90	90	0	-	-
group	02	90	90	0	-	-
	03	90	90	0	-	-
	04	Discontinued	-	-	-	-
	05	90	90	11	LU,C,S,R	Oral diphenhydramine SABA
	06	90	90	14	AP,S,R,C,GU	Oral diphenhydramine SABA
	07	90	90	3	LU	Oral diphenhydramine
	08	90	90	-	-	-
Non-anaphylactic	09	90	90	0	-	-
	010	90	90	0	-	-
group	011	90	90	0	-	
	012	90	90	0	-	-
	013	90	90	0	-	-

LU: localized urticaria; AP: abdominal pain; C: coughing; GU: generalized urticaria; S: sneezing; R: rhinorrhea; SABA: short acting βagonists

Table 8. Results of skin prick test and level of specific IgE to wheat before and after oral immunotherapy (OIT) in patients with wheat allergy

Subject ID		Wheat-SPT wheal diameter(mm)at study entry	Wheat-SPT wheal diameter (mm)after completing maintenance phase	Wheat-specific IgEat study entry (kU/L)	Wheat-specific IgE after completing maintenance phase (kU/L)
Anaphylactic	01	8	5	+6(>100)	+5(84.9)
group	02	10	6	+6(>100)	+5(83.6)
	03	10	10	+6(>100)	+5(90.4)
	04	8	Discontinued	+6(>100)	Discontinued
	05	10	6	+6(>100)	N/A
	06	8	6	+6(>100)	N/A
	07	8	6	+4(31.6)	+3(9.3)
	08	10	7	+6>100	+5(80)
Non-	09	7	5	+6(>100)	+5(93.1)
anaphylactic	010	5	4	+4(19.2)	+4(19.2)
group	011	15	11	+4(19.9)	N/A
	012	10	8	+5(83.5)	+3(10.7)
	013	8	6	N/A	N/A

N/A: not available; SPT: skin prick test

and 9 mm (min=5, max=15 mm), respectively. Mean duration of OIT in anaphylactic and non-anaphylactic group was 94.6 162.4 days, respectively. After this period, mean wheal diameter of skin prick test was 6.6 mm (range 5-10 mm) for 7 anaphylactic and 6.8 mm (range 4-11 mm) for 5 non-anaphylactic patients (Table 8). The Decrease of the wheal diameter in anaphylactic group (p=0.003) and in non-anaphylactic group (p=0.011) was statistically significant. Due to some technical issues, the results of specific IgE level to wheat for some patients are not available yet.

OFC

Our patients underwent OFC with 52 g of bread after completing maintenance phase. All of them passed OFC successfully and were regarded as being in desensitized state. After that, patients were asked to ingest wheat products freely but they had to eat at least 5.2 g wheat protein daily without interruption.

DISCUSSION

Wheat is one of the main ingredients in our daily diet; hence, avoiding foods containing wheat is very difficult. Moreover, accidental direct ingestion of these foods may cause allergic symptoms. On the other hand it can be ingested as a hidden ingredient in many products. Therefore, performing OIT can be very beneficial to these patients and can improve their quality of life. In this study we performed OIT for 13 patients with wheat allergy to evaluate its safety and efficacy. By the end of the study fortunately all of our patients could ingest foods containing wheat products without any limitations, which was a very satisfying result for patients and their family. This study showed OIT could be one of the best ways for managing patients with wheat allergy although more studies should be performed for establishing these results. Recently, OIT has been used to increase the tolerability of food allergic patients. Several investigations on OIT for milk[17, 18], egg[19, 20] and peanut[21-23] allergy have reported satisfying results; however, according to scientific evidence, there have been a few studies on wheat-OIT. Some of them are as follows:

Nucera et al. in 2003 reported a 7-year-old girl with IgE-mediated allergy to wheat who underwent a specific oral desensitization by using the pure solution of semolina and pasta. After completion of the the desensitization, she could tolerate 50 g of bread without any complications [11].

Shoichiro Taniuchi et al. performed oral

desensitization on 20 wheat-allergic children by applying hypoallergenic wheat as cupcakes for 8 months and then with conventional wheat as "undo" noodle for 9 months, lastly the study was finished by 100 g of conventional wheat. After completing the study, researchers concluded that oral desensitization using hypoallergenic wheat could induce wheat tolerance in patients with a immediate-type allergy to wheat [12].

Ayumi Fujino and Kazuyuki Kurihara reported on performing rush specific oral tolerance induction for two children, an 8-year-old girl and a 6-year-old boy, with severe wheat allergy. The ending dose was 5.6 g of wheat protein [10].

Mayumi Sugimoto et al. performed rush oral immunotherapy for 101 children with egg, milk and/or wheat allergy and followed them up for one year. In this study 12 patients had wheat allergy, 87.5% of which achieved the target dose during rush phase. During first year of maintenance, 85.7% on wheat OIT ingested one serving of wheat as a staple food [24].

Motohiro Ebisawa et al. in Sagamihara National Hospital in Japan have been conducting wheat OIT on patients with wheat allergy, the results of which have been successful. They used noodle for wheat OIT, then after completing the maintenance phase wheat tolerance is checked in their patients by OFC 2 weeks after wheat avoidance [13-14]. Regarding the fact that their protocol proved to be satisfyingly practical, we decided to use it in our research with slight modifications their method. Considering that bread is widely consumed and highly available in our country, Iran, we preferred to use it in our OIT study.

The current study enrolled a number of patients with anaphylactic and non-anaphylactic reaction after wheat ingestion. One feature of our study was to apply different protocols for each group. Difference between two methods was in build-up phase. ROIT was used in the hospital for a short period of time in anaphylactic-group due to the possibility of occuring severe reactions during build-up phase. In non-anaphylactic group build-up phase was done at home to reduce hospital costs and patient's discomfort.

It is quite evident that OIT is an effective approach in food allergy, although, patients may experience symptoms during this treatment especially through initial escalation and build-up phases[11]. For evaluating the safety of this method, the sign and symptoms of patients during immunotherapy were reviewed. The results proved seven of eight anaphylactic patients experienced allergic symptoms during build-up phase but the symptoms were observed only in 29.6% of applied doses, 94.3% of which were mild reactions. On the other hand, four out of five non-anaphylactic patients could complete build-up phase successfully without any reactions. The incidence of symptoms was very low during maintenance phase. Some mild reactions were observed in 3 patients of anaphylactic group during first month of maintenance phase. The symptoms occurred just in anaphylactic patients with severe wheat allergy. Our results indicated, if patients are properly selected and the appropriate protocol is prescribed for them, wheat OIT measure which have been used in our study can be relatively safe. However, we suggest that build-up phase of OIT for patients with a history of severe reactions must be performed in the hospital as rush method. According to our study, 100% of patients who completed maintenance phase became desensitized and they could ingest wheat products freely in comparison with the other studies of OIT that on average 50% to 75% of patients were desensitized [25].In comparison to the results of above studies on wheat OIT with success ratio of about 85% [17, 24], our study seems to be an effective protocol for wheat OIT. However, it is important to consider the fact that due to the small number of subjects in our study, further studies on more wheat allergic patients should be conducted to confirm the results obtained in our study. Some wheat allergic patients may outgrow their allergies [26], therefore for evaluation of the OIT effectiveness in establishing long-lasting tolerance, it is necessary to make comparison between patients and a control group. One of the main limitations in this study was the lack of a control group, which occurred because all patients desired to be treated. Ultimately we reached the primary goal of our study, which was wheat desensitization and enhancing the reaction threshold in wheat allergic patients, but at this point we do not know whether patients have been completely desensitized to wheat and could tolerate wheat products after discontinuing the maintenance dose. Therefore, we decided to check the long-lasting tolerance in our subjects one year after beginning of the maintenance dose using OFC with two-week avoidance from eating wheat products. However, before checking the status of a patient's tolerance, the subject should not discontinue the maintenance dose. Nevertheless, even if patients could not reach the tolerance, it is a great satisfactory

for them to reach a state of desensitization.

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