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The Efficacy of a New Protocol of Oral Immunotherapy to Wheat for Desensitization and Induction of Tolerance

Samin Sharafian[1], Aliakbar Amirzargar[2,3], Mohammad Gharagozlou[4], Nima Parvaneh[4], Mansoureh Shariat[4], Marzieh Tavakol[5,6], and Masoud Movahedi[4]

[1] Department of Immunology and Allergy, Mofid's Children Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[2] Department of Immunology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran
[3] Molecular Immunology Research Center, Tehran University of Medical Sciences, Tehran, Iran

[4] Division of Allergy and Clinical Immunology, Department of Pediatrics, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran
[5] Non-communicable Diseases Research Center, Alborz University of Medical Sciences, Karaj, Iran
[6] Department of Allergy and Clinical Immunology, Imam Ali Hospital, Alborz University of Medical Sciences, Karaj, Iran

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ABSTRACT

Oral immunotherapy (OIT) is a novel approach to desensitization and tolerance induction in food allergy patients. This study aimed to design and implement a new wheat OIT protocol, evaluate its efficacy in tolerance induction, and assess specific immunoglobulin-E (IgE) and regulatory T cell changes.

From 2015 to 2017, 26 patients with confirmed IgE-mediated hypersensitivity to wheat were treated via oral immunotherapy (OIT). Patients with prior anaphylactic episodes underwent OIT using the rush method. Specific IgE concentrations and the number of regulatory T cells (CD4+ CD25+ FOXP3+ T cells) were measured using Allergy Screen immunoblot assay and flow cytometry, respectively. This study was registered in the Iranian Registry of Clinical Trials (IRCT20181220042066N1).

The results revealed success rates of 100% and 93.3% for desensitization and tolerance. Specific IgE was significantly reduced after 12 months of OIT. No significant change in regulatory T cell numbers was observed.

In view of the promising findings of this study, the proposed OIT protocol could be viewed as an effective and valuable method to induce tolerance and desensitization in wheat allergic patients.

Keywords: Immune tolerance; Immunoglobulin E; Immunologic desensitization; Regulatory T-lymphocytes; Wheat hypersensitivity

Corresponding Author: Masoud Movahedi, MD; Division of Allergy and Clinical Immunology, Department of Pediatrics, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran. Tel: (+98 912) 1096 714, Fax: (+98 21) 6642 8996, E-mail: movahedm@sina.tums.ac.ir

INTRODUCTION

Food allergy (FA) is one of the most problematic issues in children. Approximately 10% population has food allergies worldwide, a constantly rising number. The severity of allergic reactions and the possibility of avoidance as the primary therapeutic approaches are considered the most challenging aspects of food allergy.[1]

Food avoidance is not a perfect therapeutic approach owing to the risk of allergic reactions resulting from the accidental intake or exposure to an allergenic substance.[2] Patients with a FA might also suffer from nutritional deficiencies.[3] Some therapeutic approaches have been developed to overcome these problems, among which oral immunotherapy (OIT) has recently received special attention. The final goal of treating FA is tolerance induction in patients, as it would be safe to use the culprit food without the necessity of receiving it daily.[4]

As a significant ingredient of human food, wheat could induce IgE mediated or/and non-IgE mediated allergic reactions.[5,6] IgE-mediated hypersensitivity to wheat affects up to 1% of the population in different regions.[7,8] Furthermore, wheat has been considered an essential; for inducing anaphylaxis allergenic reactions in children.[9] A wheat-free diet is the primary intervention to manage the wheat allergy. In addition to prescribing medications such as antihistamines and glucocorticoids to relieve symptoms, epinephrine is also prescribed for anaphylactic patients to support the accidental exposure.[5]

Regulatory T cells (Tregs), a subgroup of $CD4^+$ T cells that play a crucial role in T-cell homeostasis and immune regulation, inhibit the activation and proliferation of autoreactive lymphocytes. It is considered that Tregs can induce tolerance in OIT.[10] Moreover, allergic sensitization and reactions could be suppressed via Tregs function.[11] To our knowledge, a few studies have been published concerning OIT to wheat.[12,13] This study aimed to devise and implement a new protocol of OIT in patients with IgE-mediated reactions to wheat to evaluate its efficacy in tolerance induction and its impact on alteration of specific IgE and Treg numbers.

MATERIALS AND METHODS

Participants

Twenty-six patients with severe immediate hypersensitivity to wheat were referred to the Division of Allergy and Clinical Immunology, Department of Pediatrics, Children's Medical Center, Tehran, Iran, between 2015 and 2017 entered this clinical trial. Inclusion criteria were as follows: age of more than 4 years, a positive clinical history of allergy to wheat, a positive specific IgE to wheat (in vivo or in vitro tests), and wheat allergy confirmed by double-blind, placebo-controlled food challenge (DBPCFC). Patients' or their parents' dissatisfaction with performing DBPCFC was the main exclusion criterion. Moreover, patients were asked to stop any medicines they utilized, interfered with the skin prick test (SPT), or DBPCFC interpretation. Hence the impossibility of discontinuing the medications that interacted with epinephrine injection, such as beta-blockers, was considered another criterion of exclusion.

Additionally, patients were thoroughly examined when performing the procedure of OFC or DBPCFC; they were excluded if there were viral or bacterial infectious diseases and unstable or uncontrolled asthma. Signed informed consent was obtained from all patients or their parents. The Ethics committee approved this clinical trial at the Tehran University of Medical Sciences (IR.TUMS.MEDICINE.REC.1396.3196). The Iranian Registry also approved it for Clinical Trials (IRCT20181220042066N1).

Study Design

After recording the demographic, past medical information, and clinical history, patients underwent a thorough physical examination. Six milliliters (6 mL) of blood were taken from the patients before DBPCFC. The serum-specific IgE to wheat, in addition to the count and percent of Tregs [$CD4^+$ $CD25^+$ (DAKO), $FOXP3^+$ (Exbio)], were evaluated utilizing the AllergyScreen system (Mediwiss, Germany) and Partec PAS flow cytometer (Germany), respectively before and after OIT. DBPCFC was performed for all patients using the prepared pieces of bread with wheat and rice flour (as a placebo) for two days according to the doses illustrated in Table 1. Set pieces of bread containing wheat flour or placebo were randomly given to the patient on two consecutive days by a third blinded allergist. To do DBPCFC, the patients were

hospitalized at Children's Medical Center. Gradual doses increase was carried out every 20 minutes, provided the patient manifested no symptoms. All facilities and emergency medications were provided for managing the anaphylactic reactions.

Build-up Phase

OIT using the rush method was performed for 26 patients. The diagram of the OIT protocol is shown in Figure 1. The patients' reactions in DBPCFC were graded based on the severity of symptoms observed during the treatment process. Patients received premedication with cetirizine and montelukast started three days before the beginning of the study and continued for 6 months. Additionally, methylprednisolone was administrated during hospitalization. Patients were admitted to getting the early phase of rush OIT. In the rush method, patients were given a specific quantity of sandwich bread 10% (Senan company, Iran) containing a known amount of wheat protein twice daily. The doses used in the build-up phase were similar to those of the challenge protocol. Despite the initial decision to select the first dose based on the results of the OFC, due to the high risk in anaphylactic patients, the initial amount of immunotherapy in every patient began with the first dose of protocol (0.04 g). If the patient lacked severe symptoms and tolerated the bread, its amount was

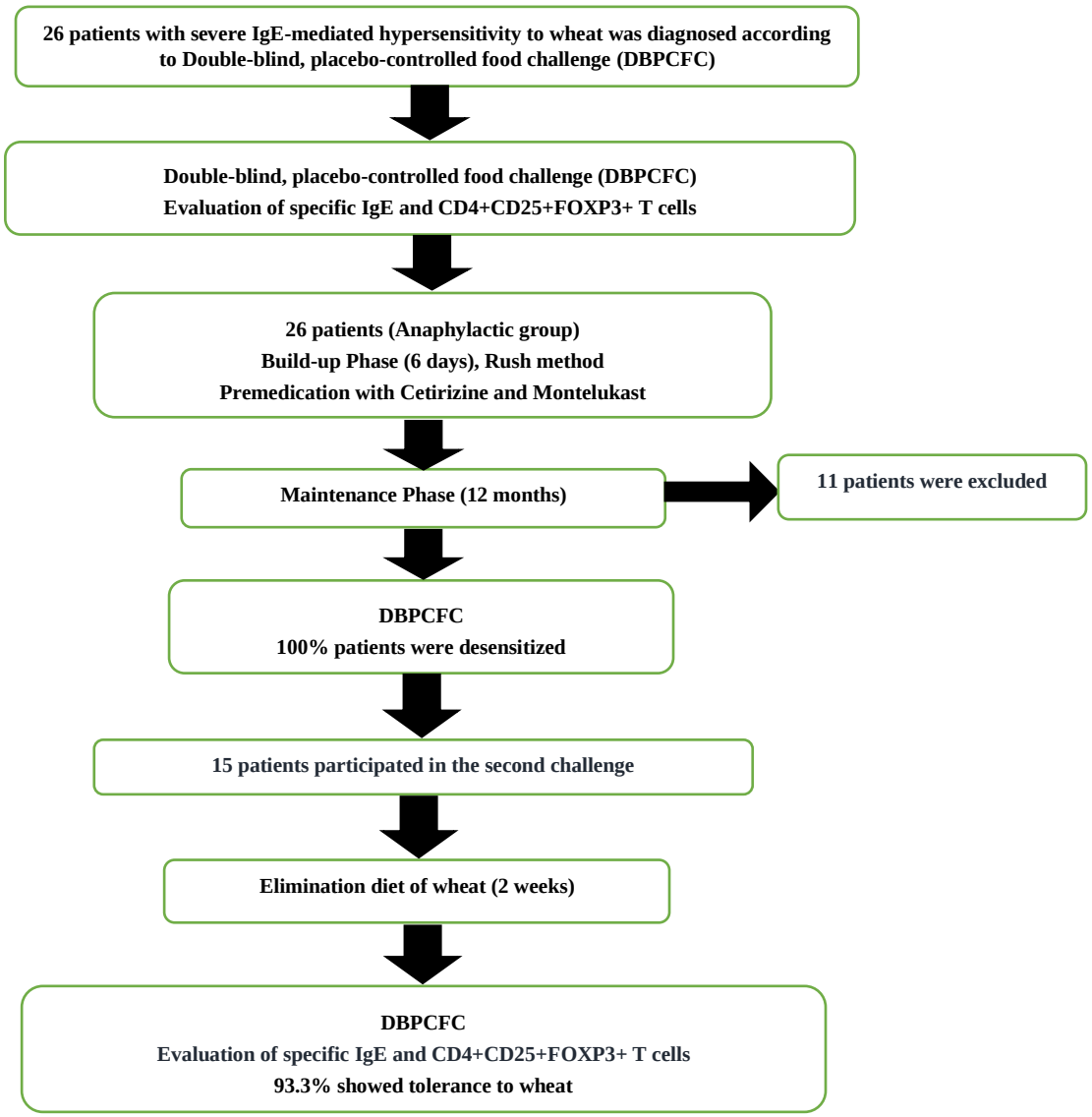

Figure 1. Diagram of oral immunotherapy (OIT) protocol.

Table 1. The time and doses of double-blind, placebo-controlled food challenge (DBPCFC)

Level	1	2	3	4	5	6	7	8	9	10	11
Time (Min)	0.00	20:00	40:00	60:00	80:00	100:00	120:00	140:00	160:00	180:00	200:00
Dose (g)	0.04	0.08	0.168	0.336	0.624	1.04	1.456	2.08	3.12	4.16	5.2

Minute (Min); Gram(g)

increased to the target of 52 grams of 10 percent sandwich bread (equivalent to 5.2 grams of wheat protein). The next dose of wheat was adjusted for symptoms and tolerated the bread; its amount was increased to the target of 52 grams of 10 percent sandwich bread (equivalent to 5.2 grams of wheat protein).The next dose of wheat was adjusted considering the severity of the reaction after administration of the previous doses. In the case of mild reactions or one episode of a moderate attack, the amount of wheat was increased based on the protocol. However, in two events of reactions with moderate symptoms, the previous dose was repeated. Three moderate reactions or even one event with severe symptoms led to a decrease in the amount of wheat to the last tolerated dose. Complete management of anaphylactic reactions, including intramuscular injection of epinephrine, parenteral methylprednisolone, oral cetirizine or diphenhydramine, and inhaled salbutamol, was performed for patients who experienced anaphylaxis. The protocol of the rush method is shown in meticulous detail in Table 2. All patients avoided any physical activities following each dose of desensitization.

Table 2. The protocol of the rush method in the hospital for anaphylactic patients

	Activities	Time
First Day	Admission	9:30
	Blood Sampling and Skin Prick Test (SPT)	10:00
	Eating Bread 0.5 mg/Kg Methylprednisolone	10:00
	Lunch	12:00
	Eating bread	14:30
	Dinner	18:00
	Medications (Cetirizine and Montelukast)	18:30
Second –Fifth Day	Breakfast	7:00
	0.5 mg/Kg Methylprednisolone	8:00
	Eating bread	9:00
	Lunch	12:00
	Eating bread	14:00
	Dinner	18:00
	Medications (Cetirizine, Montelukast and 0.5 mg/Kg Methylprednisolone)	18:30
Sixth Day	Breakfast	7:00
	0.5 mg/Kg Methylprednisolone	8:00
	Eating bread	9:00
	Lunch	12:00
	Discharge	14:30

Maintenance Phase

After the build-up phase, all patients underwent a 12-month maintenance phase. Based on the inclusion and exclusion criteria, patients were called at known intervals and were asked to participate in the next part of the study. Participants consumed at least 52 grams of 10 percent sandwich bread in this stage for up to 3 months. Then, in addition to 52 grams of 10 percent sandwich bread, patients could use any products containing wheat until 12 months. Afterward, a wheat-free diet was administered for 2 weeks for fifteen patients.[14] Eleven patients did not participate in this phase. Then, DBPCFC was performed for all participants at the end of the study. The patients' history and physical examination were recorded. In case of adverse reactions, including urticaria, wheezing, breathlessness, vomiting, and abdominal cramps, DBPCFC was stopped, and the subject was considered intolerant. Patients were considered "desensitized" if they tolerated 52 grams of 10 percent sandwich bread without causing an adverse reaction after the 12-month maintenance phase and if they continued to be asymptomatic to the same amount of wheat protein after a two-week wheat-free diet were considered tolerant. The results were recorded at all stages and compared with the initial values of the study.

Statistical Analysis

First, descriptive statistics, including mean and standard deviation, were determined. Furthermore, independent t-tests and Mann-Whitney were utilized to reveal the difference in quantitative variables between the two separate groups. Moreover, paired t-tests and Wilcoxon signed-rank tests were applied to compare the variables at baseline and after 12 months. The data analysis was performed using SPSS software version 20 (Armonk, IBM Corp, NY). A *p*-value less than 0.05 was regarded as a significant level. Excel was used for drawing the graphs.

RESULTS

Eleven patients (73.3%) were male. The mean age of participants was 74.40 months (48 -132 months).

The mean age of the first symptoms was 8.46 months. Among patients with anaphylactic reaction to wheat, the frequency of asthma, atopic dermatitis, and allergic rhinitis was 8, 1, and 3, respectively. A positive history of another FA was observed in ten patients. The average duration of the build-up phase was 12 days. Regarding the durability of tolerance, 14 out of 15 (93.3%) patients who were re-evaluated one year after treatment showed patience to wheat, and only one patient (6.7%) failed to sustain tolerance. Of course, this patient only showed urticaria while she had manifested anaphylactic reactions after wheat consumption before desensitization. All tolerated patients consumed wheat products without allergic reactions after three years. Table 3 presents the immunological changes at baseline and after 12 months of OIT. The mean concentrations of specific IgE in wheat were 90.40 IU/mL and 66.50 IU/mL, baseline and after OIT, respectively (p=0.011, Figure 2a). The number of $CD25^+$ T cells in flow cytometry significantly changed after Immunotherapy (P=0.001). However, the CD4+ and $FOXP3^+$ T cells population did not follow the same trend (Figure 2b).

The median doses of allergic reactions in the initial and final challenge were 0.08 (0.4-1.04 g) and 2.08 g, respectively. Allergic manifestations that occurred before and during the initial challenge included cutaneous (urticaria and itching), respiratory (wheezing, shortness of breath, nasal congestion, and itching), gastrointestinal (vomiting and abdominal pain), and cardiovascular (hypotension) symptoms, among which, skin involvement was the most prevalent.

All patients who underwent OIT with the rush method successfully passed this phase. At the end of this phase, they could tolerate 52 grams of 10 percent sandwich bread (5.2 grams of wheat protein). The average duration of the dose increase was 15.33 days (8-30). Adverse reactions were seen in 75 (21.4%) out of 349 doses.

During the desensitization period, patients experienced various reactions, including cutaneous, respiratory, gastrointestinal, cardiovascular, and systemic (anaphylactic) manifestations at different wheat protein doses. The highest numbers of reactions were observed after the fourth, fifth, and sixth doses. One hundred and sixty reactions occurred during the build-up phase, among which skin involvement (40.6%) was the most frequent, followed by anaphylaxis (23.75%), respiratory symptoms (23.1%),

and gastrointestinal manifestations (8.75%), and cardiovascular symptoms (3.75%).

Oral diphenhydramine syrup was the most commonly used medication and was prescribed for 64 of 160 (40%) reactions. Salbutamol spray was used on 39 occasions (24.37%). During the build-up phase, 38 anaphylactic reactions (23.8%) were reported, managed by intramuscular injection of epinephrine, methylprednisolone, cetirizine, diphenhydramine, and salbutamol.

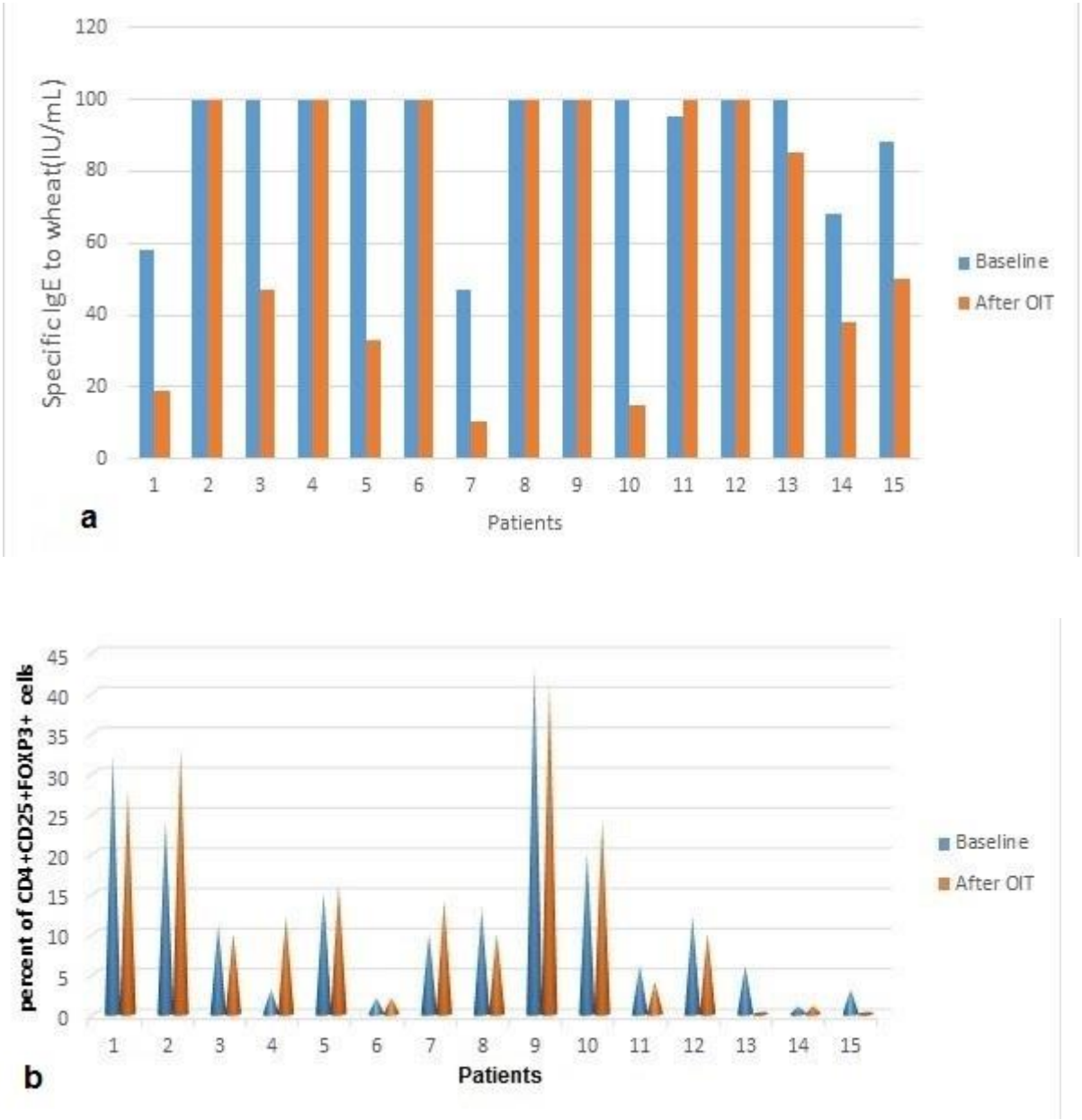

Figure 2. The specific immunoglobulin-E (IgE) concentration (2a) and the percent of CD4+CD25+FOXP3+ cells (2b) at baseline and after 12 months. Oral Immunotherapy (OIT)

Table 3. Immunological changes at baseline and after 12 months of oral immunotherapy

	Baseline	After OIT	*p*
Sex (Male/Female)	11 / 4		
Age (Months)	74.4 ± 18.81		
Age of the first symptoms	8.46 ± 2.09		
White Blood Cells/µL*	8706 ± 2317	8169 ±2017	0.37
Lymphocytes /µL*	3627 ± 1295	3496 ±1098	0.65
CD4 /µL*	1398 ± 506	1349 ±529	0.67
CD25 /µL**	20(11,43)	89(40,336)	**0.001***
FOXP3 /µl*	125.45 ± 43.11	125.40 ± 91.82	0.99
CD4+CD25+FOXP3+ (%)**	11(3,20)	10(2,24)	0.94
Specific IgE (IU/mL)*	90.40 ±17.69	66.50 ±36.66	0.011*

*Mean±SD; **Median (Q1, Q3), Forkhead box P3 (FOXP3), Oral immunotherapy (OIT)

DISCUSSION

This study's findings showed 100 % and 93.3% success rates for desensitization and tolerance in patients with IgE-mediated wheat allergy. Compared with the baseline level, specific IgE significantly decreased at the end of the treatment, while no notable change was observed in the number of Tregs.

Although oral desensitization is associated with favorable clinical outcomes and improved quality of life, it is likely to cause allergic reactions, especially in the build-up phase.[15] Mild to moderate symptoms, which could often be easily controlled, have been reported. More severe allergic reactions such as angioedema, abdominal pain, wheezing, respiratory distress, and gastrointestinal problems might also occur.[16] In our study, 45.8% of patients displayed allergic reactions, 76.2% of which were mild to moderate. Epinephrine was administrated in 23.8% of patients who showed severe manifestations. The prevalence of reported adverse reactions during OIT has not been the same in different studies. Sato et al. reported that adverse reactions to wheat occurred in 26.4% and 6.8% of cases in the rush and build-up and maintenance phases, respectively. They also declared that intramuscular epinephrine was administrated three times (0.04%) for severe reactions in the build-up and maintenance phases.[17] In another study by del Rio et al, et al. six mild reactions (6.25%) were recorded in the up-dosing phase of OIT for wheat.[18] The study by Hoffman et al. showed adverse reactions in 93%, 46%, and 3.5% during the escalation, build-up, and maintenance phases of peanut OIT, respectively. Besides, two of their patients were prescribed epinephrine owing to critical manifestations.[19] In a study by Rekabi et al, 75% of patients who experienced anaphylactic reactions to wheat received intramuscular epinephrine.[20] Consequently, this therapeutic measure should be done under the supervision of a specialist in allergy with proper equipment and medications to treat adverse reactions.

Various studies have reported a 36 to 90% success rate for OIT.[21] In our study, all enrolled patients completed the treatment phases, which means the applied protocol could be used as an alternative method to the previous ones.

There are two possible outcomes for immunotherapy, both of which are more beneficial than an elimination diet. The first one is desensitization, which means that as long as patients consume specific minimum daily dosages of food allergen, they would remain unresponsive to it.[21] The majority of studies so far reached the level of oral food desensitization. In the present study, 15 of 15 (100 %) were successfully desensitized using wheat without any problem. The second outcome is tolerance which is challenging to be achieved.

Contrary to desensitization, there is no need to constantly consume the culprit food to keep away from the adverse reactions in a patient who achieves tolerance. In other words, it is safely possible to discontinue eating the allergenic food even for a long

time. Fifteen patients out of 26 in the current survey participated in the final challenge (confirming tolerance). Among them, 14 patients tolerated wheat after two weeks of the elimination diet, which was considerably more prominent than in previous studies[12,13]. In the study carried out by Khayatzadeh et al, all patients reported consuming the wheat products after OIT, but the tolerance rate was not investigated.[13] Khalili et al also conducted a survey in which 10 patients who had previously undergone OIT to wheat went through a 2-week wheat avoidance. Researchers then performed OFC for wheat in the study group and realized that 4 (40%) patients achieved tolerance, and 6 (60%) of them experienced fewer symptoms than before OIT.[12] Few studies have been concentrated on the induction of tolerance via oral administration of wheat, and most of them were conducted by enrolling a small sample size.

Our study's findings demonstrated that 14 patients (93.3%) successfully passed the final step of DBPCFC and showed tolerance. Only one patient experienced flushing after using a dose of 2.8 g of wheat protein. One of the reasons the higher proportion of desensitization and tolerance induction in our study could be attributable is the amount of wheat protein at the starting point and the increasing amount rate. In comparison with the baseline profile of symptoms, adverse reactions to the treatment procedure were mild. Fewer adverse reactions could be due to the administration of cetirizine, montelukast, and methylprednisolone in the build-up phase. Montelukast as a particular antagonist of cysteinyl-leukotriene receptor 1 and cetirizine as a new generation histamine H1 receptor antagonists have immunomodulatory effects and could help OIT.[22-24]

A further finding of the current research was a significant decrease in the specific IgE to wheat following OIT. In line with this study, Sato et al. found substantial changes in the level of specific IgE after 2 years.[17] At the end of the survey done by Khayatzadeh et al, significant changes in the specific IgE levels were found, and SPT showed a considerable decrease in the wheal size of wheat.[13] Khalili et al.'s findings showed significant changes in specific IgE after OIT.[12]

The process of food tolerance is associated with modifications in the immune system, including a decrease of mast cell activity markers (e.g., reducing the wheal size in SPT), basophil activation tests change, alterations in specific IgE, and detailed IgG4 profiles as well as stimulation of Tregs.[25] No significant difference was found between the Treg count before and after desensitization. Contrary to our findings, Syed et al. reported a substantial increase in FOXP3 expression and induced regulatory T cells intolerant patients to peanuts, assessed 24 and 27 months after OIT.[26] This might be due to the different intervals between OIT and investigating these parameters in the surveys.

This study's innovative and different OIT protocol was associated with a 100% success rate in the induction of desensitization and 93.3% success in tolerance development. Compared to the previous studies[12,13], anaphylaxis and other immediate-hypersensitivity reactions were fewer in the maintenance phase. The tolerance rate was also investigated and confirmed at the end of the maintenance phase. One of the strengths of this study was applying the rush method in the build-up phase in patients.

This study's promising results demonstrated a 100 % and 93.3% success rate for desensitization and tolerance to wheat after OIT, respectively. All patients continued to have a wheat-containing diet. Patients' quality of life has dramatically improved, albeit standardized questionnaires for quality of life should be used to document this finding. Considering the proper and practical protocols proposed in this study and consuming bread as a ubiquitously available wheat-containing product, it seems that desensitization with this method could be done under the supervision of allergists as a therapeutic or investigational approach for wheat allergic patients.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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REFERENCES

1. Sicherer SH, Sampson HA. Food allergy: A review and update on epidemiology, pathogenesis, diagnosis, prevention, and management. J Allergy Clin Immunol. 2018;141(1):41-58.

2. Yu W, Freeland DMH, Nadeau KC. Food allergy: immune mechanisms, diagnosis and immunotherapy. Nat Rev Immunol. 2016;16(12):751-65.
3. Hobbs CB, Skinner AC, Burks AW, Vickery BP. Food Allergies Affect Growth in Children. J Allergy Clin Immunol Pract. 2015;3(1):133-4.e1.
4. Khoriaty E, Umetsu DT. Oral Immunotherapy for Food Allergy: Towards a New Horizon. Allergy Asthma Immunol Res. 2013;5(1):3-15.
5. Cianferoni A. Wheat allergy: diagnosis and management. J Asthma Allergy. 2016;9:13-25.
6. Elli L, Branchi F, Tomba C, Villalta D, Norsa L, Ferretti F, et al. Diagnosis of gluten related disorders: Celiac disease, wheat allergy and non-celiac gluten sensitivity. World J Gastroenterol. WJG. 2015;21(23):7110-9.
7. Leonard MM, Vasagar B. US perspective on gluten-related diseases. Clin Exp Gastroenterol. 2014;7(2):25-37.
8. Ricci G, Andreozzi L, Cipriani F, Giannetti A, Gallucci M, Caffarelli C. Wheat Allergy in Children: A Comprehensive Update. Medicina (Kaunas, Lithuania). 2019;55(7):400.
9. Barzegar S, Rosita A, Pourpak Z, Bemanian MH, Shokouhi R, Mansouri M, et al. Common Causes of Anaphylaxis in Children: The First Report of Anaphylaxis Registry in Iran. World Allergy Organ J. 2010;3(1):9-13.
10. Wang P, Zheng SG. Regulatory T cells and B cells: implication on autoimmune diseases. Int J Clin Exp Pathol. 2013;6(12):2668-74.
11. Curotto de Lafaille MA, Lafaille JJ. Natural and adaptive foxp3+ regulatory T cells: more of the same or a division of labor? Immunity. 2009;30(5):626-35.
12. Khalili A, Khayatzadeh A, Ebrahimi M, Rafiemanesh H, Azizi G, Movahedi M. Evaluation of Tolerance in Patients With Type-1 Hypersensitivity Reaction to Wheat After Oral Immunotherapy. J Investig Allergol Clin Immunol. 2016;26(5):339-40.
13. Khayatzadeh A, Gharaghozlou M, Ebisawa M, Shokouhi Shoormasti R, Movahedi M. A Safe and Effective Method for Wheat Oral Immunotherapy. Iran J Allergy Asthma Immunol. 2016;15(6):525-35.
14. Nowak-Wegrzyn A SH, Sicherer SH. Food Allergy and Adverse Reactions to Foods. In: Kliegman R, editor. Nelson Textbook of Pediatrics. 21 ed. Philadelphia, PA: Elsevier; 2020. p. 1241.
15. Vazquez-Ortiz M, Turner PJ. Improving the safety of oral immunotherapy for food allergy. Pediatr Allergy Immunol. 2016;27(2):117-25.
16. Khoriaty E, Umetsu DT. Oral Immunotherapy for Food Allergy: Towards a New Horizon. Allergy Asthma Immunol Res. 2013;5(1):3-15.
17. Sato S, Utsunomiya T, Imai T, Yanagida N, Asaumi T, Ogura K, et al. Wheat oral immunotherapy for wheat-induced anaphylaxis. J Allergy Clin Immunol. 2015;136(4):1131-3.e7.
18. Rodriguez del Rio P, Diaz-Perales A, Sanchez-Garcia S, Escudero C, do Santos P, Catarino M, et al. Oral immunotherapy in children with IgE-mediated wheat allergy: outcome and molecular changes. J Investig Allergol Clin Immunol. 2014;24(4):240-8.
19. Hofmann AM, Scurlock AM, Jones SM, Palmer KP, Lokhnygina Y, Steele PH, et al. Safety of a peanut oral immunotherapy protocol in children with peanut allergy. J Allergy Clin Immunol. 2009;124(2):286-91, 91.e1-6.
20. Rekabi M, Arshi S, Bemanian MH, Rekabi V, Rajabi A, Fallahpour M, et al. Evaluation of a new protocol for wheat desensitization in patients with wheat-induced anaphylaxis. Immunotherapy. 2017;9(8):637-45.
21. Pajno GB, Cox L, Caminiti L, Ramistella V, Crisafulli G. Oral Immunotherapy for Treatment of Immunoglobulin E-Mediated Food Allergy: The Transition to Clinical Practice. Pediatr Allergy Immunol Pulmonol. 2014;27(2):42-50.
22. Nankervis H TK, Delamere FM, et al. Scoping systematic review of treatments for eczema. Southampton (UK): NIHR Journals Library; 2016 May. (Programme Grants for Applied Research, No. 4.7.) Chapter 11, Systemic immunomodulatory agents. Available from: https://www.ncbi.nlm.nih.gov/books/NBK363140/.
23. de Montjoye L, Herman A, Nicolas JF, Baeck M. Treatment of chronic spontaneous urticaria: Immunomodulatory approaches. Clin Immunol. 2018;190:53-63.
24. Parisi GF, Leonardi S, Ciprandi G, Corsico A, Licari A, Miraglia del Giudice M, et al. Cetirizine use in childhood: an update of a friendly 30-year drug. Clin Mol Allergy. 2020;18(1):2.
25. Ponce M, Diesner SC, Szepfalusi Z, Eiwegger T. Markers of tolerance development to food allergens. Allergy. 2016;71(10):1393-404.
26. Syed A, Garcia MA, Lyu SC, Bucayu R, Kohli A, Ishida S, et al. Peanut oral immunotherapy results in increased antigen-induced regulatory T-cell function and hypomethylation of forkhead box protein 3 (FOXP3). J Allergy Clin Immunol. 2014;133(2):500-10.