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Oral Immunotherapy in Children: Ige-Dependent Food Allergy to Milk or Wheat

* Fasihe Mazandarani [1], Hamid Ahanchian [2], Nasrin Moazzen [3]

[1] Pediatric Resident in Mashhad University of Medical Sciences, Mashhad, Iran.

[2] Clinical Research Development Unit of Akbar Hospital, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.
[3] Clinical Research Development Unit of Akbar Hospital, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.

Abstract

Oral Immunotherapy (OIT) is an effective strategy for improving food allergy tolerance. OIT has been introduced as a novel immune-modulating medication for food allergies. Other immunomodulatory approaches, such as sublingual (SLIT) or epicutaneous (EPIT) immunotherapy, may be less effective due to lower frequencies of systemic responses. Wheat and milk have lately been identified as a more prevalent cause of food-induced anaphylaxis than previously thought, particularly in young children worldwide. An immunoglobulin E (IgE)-dependent pathway may be responsible for wheat or milk allergy. The goal of our study was to offer a comprehensive evaluation of the effects of OIT in children with IGE-dependent food allergies to milk or wheat. Keywords related to OIT, food allergy, milk, wheat, and children were searched in MEDLINE, PubMed, Google Scholar, and ScienceDirect databases. Although oral immunotherapy for wheat allergy has recently been proposed, research studies have had encouraging results; despite, more research is still needed to determine the optimum strategy for promoting tolerance in wheat/milk-allergic children.

Key Words: Oral immunotherapy, food allergy, children, Milk, Wheat.

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Corresponding Author:

Fasihe Mazandarani, Pediatric resident in Mashhad University of Medical Sciences, Mashhad, Iran. Email: fasihemazandarani22@gmail.com

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1- INTRODUCTION

Food allergies are becoming more common across the world. It is currently predicted that up to 5% of the European and American populations are faced with (1-3) generating significant morbidity, lowering patients' quality of life, and troubling expenses of medical treatment (4). Only rigorous dietary restriction is currently recommended as a therapy for food allergies. As a result, food allergy treatments are desperately needed. Oral immunotherapy (OIT) has emerged as a novel promising allergen-specific treatment for patients with IgE-mediated food allergy (5) , with a focus on the foods that cause severe anaphylactic responses, i.e., the most frequently and the most prevalent food allergens, such as cow's milk, peanuts, and eggs (6). Mild to severe clinical symptoms such as anaphylaxis can occur (**Fig. 1**) (7).

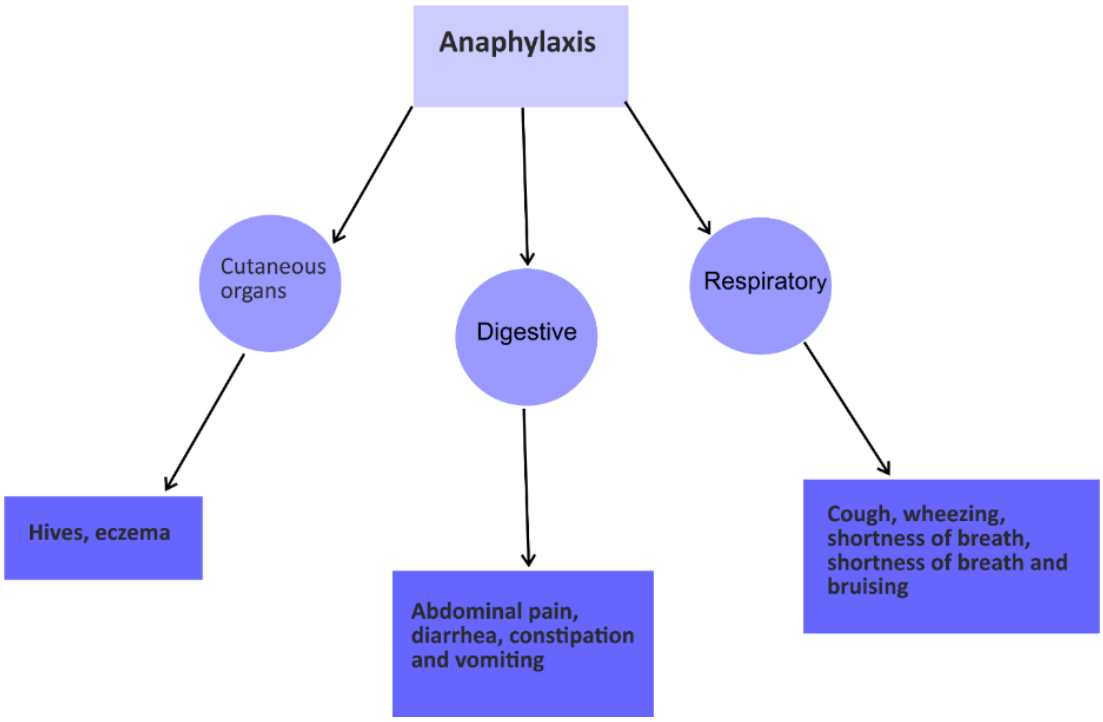

Fig. 1: Clinical symptoms of Anaphylaxis

There is a significant advancement and interest in using this therapy option for people with food allergies, as evidenced by the publications of many exploratory experiments. Before OIT becomes a widely recognized choice, there are still numerous questions to be solved and parameters to be fine-tuned. Wheat-related allergy diseases are classified as food allergies, respiratory allergies, or skin allergies, depending on the route of entry, and are treated using gastroenterological protocols in most countries. IgE-dependent wheat allergy (WA) and IgE-non-dependent wheat allergy (WA) are two types of food allergies induced by wheat ingestion (8). Wheat is one of the top five foods that children have adverse responses to. After milk and eggs, it has been recognized as the third most prevalent allergy in Germany, Japan, and Finland (9). Despite the fact that wheat proteins enter into breast milk, as demonstrated by Linn et al. in 1996, WA is frequently diagnosed in young children, although it is seldom found in babies (10). Numerous

IgE antibodies that bind to proteins from all wheat grain fractions, most typically gliadins, are identified in the blood of individuals with IgE-mediated wheat allergy. However, they are not the same proteins in various tests, and so they cannot be considered serious allergens in children with WA (11, 12). When IgE antibodies specific for a protein are discovered in a large proportion of children with WA, that protein is considered the main allergen. There are 27 wheat allergies on the World Health Organization's list (13). Many of them have yet to be determined in terms of clinical significance. rw-5 gliadin is the best-understood allergenic molecule of WA (Tri a 19) (14, 15). All patients with wheat-dependent, exercise-induced (WDEIA), 80% of children with anaphylactic symptoms after wheat consumption, and 20%–30% of children with WA and atopic eczema have the rw-5 gliadin-specific IgEs (12). A non-specific lipid transfer protein (Tri a 14) is the second allergenic molecule of WA for which commercial testing is available (nsLTP). In WA youngsters and patients with WDEIA, antibodies indicating the presence of IgE specific to (Tri a 14) are detected. They aren't very sensitive. Although there isn't enough evidence to rule out cross-reactivity with grass pollen, it's currently assumed that they don't. Their findings might aid in distinguishing wheat sensitization from pollen allergy, which is critical in individuals with high grass pollen-specific IgE levels (8). The first study on oral immunotherapy for older children with anaphylaxis provoked by wheat intake has been published in the scientific literature. In 61 percent of patients, the treatment resulted in desensitization after two years (16). More research is needed to determine the efficacy of this sort of WA therapy (8). The effectiveness of OIT in patients with cow's milk allergy was found to be 40 percent to 90 percent, with a considerable rise in the threshold intake (17-20). However, OIT is not suggested as a regular treatment for significant allergies in the recommendations since it might produce extreme adverse responses such as anaphylaxis (21). In Japan, Cow's milk allergy is the second most common food allergy among young children, after hen's egg allergy (22). Cow's milk allergy has a significant influence on the everyday and social life of children and their parents in Japan since cow's milk is served in school lunches in nursery, elementary, and junior high schools. Important factors such as the threshold for symptom induction and intensity, as well as the timing of start and severity of adverse effects, have often been unclear in prior findings on OIT for cow's milk allergy. Furthermore, because there is little research on the long-term effects of milk OIT, it is unclear if OIT causes not just desensitization but also prolonged unresponsiveness (23). As a result, the purpose of this study was to see how OIT affected children with IGE-dependent milk or wheat allergies.

2- MATERIAL AND METHODS

Using the Internet databases of PubMed, Medline, Google Scholar, and ScienceDirect, two scientists did a systematic search of the literature from 2010 to 2021. Two writers worked individually to find relevant publications, including title and abstract screening, full-text screening, and decide for final inclusion. The acceptance of manuscripts was based on the agreement of two independent reviewers. When the decision on inclusion could not be made solely on the title or abstract, studies were chosen for further full text screening. The references of the publications identified in the full text screening were manually scrutinized by one investigator for additional identification of relevant records, and this list was evaluated by the second investigator. The inclusion

technique is depicted in **Fig. 2** as a flow chart.

2-1. Inclusion criteria

a) Articles in English language.

b) Articles studying on children (5 years and older) who had been diagnosed with a food allergy or had reported having an IGE-dependent food allergy to milk or wheat.

c) Complete articles in terms of structure and content.

2-2. Exclusion criteria

a) Studies that provide duplicate data (e.g., abstracts presented at several congresses or abstracts published as a full-length paper).

b) Case or control subsets from a previously published study by the same researchers.

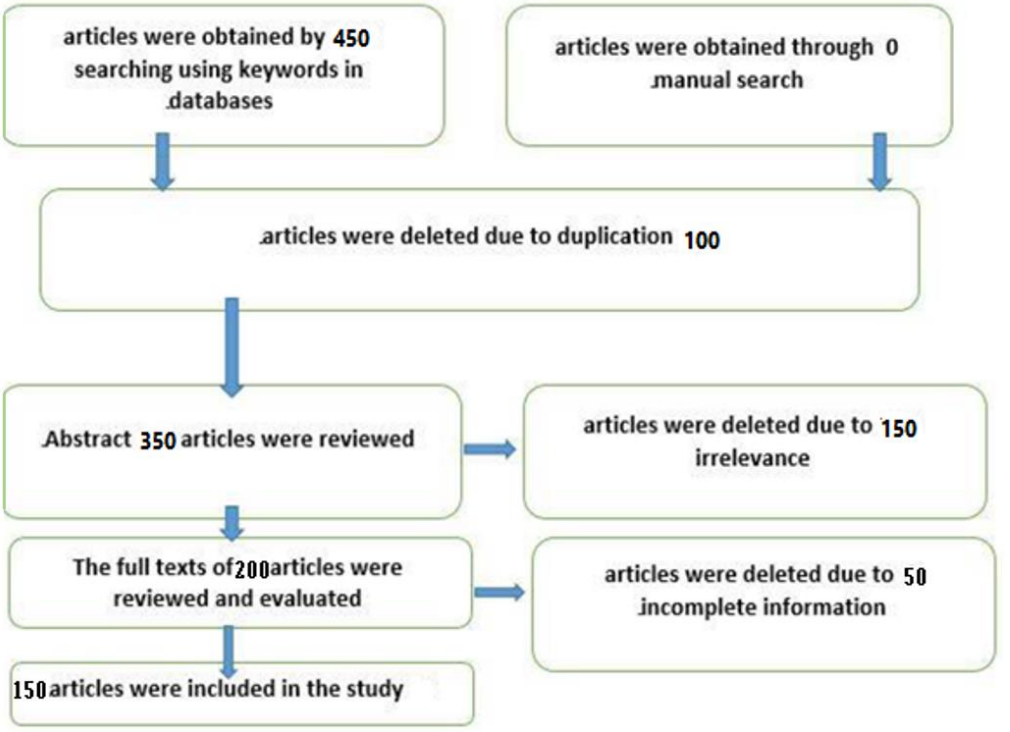

Fig. 2: Flow chart of the procedure

3- RESULTS AND DISCUSSION

The only acknowledged therapy for food allergies is to avoid the causal allergen completely (24, 25). Some of the sufferers, however, continue to experience allergic symptoms well into adulthood. Due to hunger, eating disorders, and psychological problems, as well as inadvertent exposure to cow's milk and anaphylactic responses, the food exclusion diet greatly reduces the quality of life of both patients and their families (26, 27). Furthermore, eliminating cow's milk from the diet is challenging due to the fact that it may be concealed and not always indicated in some items. Many efforts have been made to identify alternative therapies for food allergies that affect the natural course of the disease. Among these, OIT is one of the most extensively researched therapies (28-31). Other studies have shown that OIT can reduce the frequency and severity of allergic reactions, along with changing the natural course of cow's milk allergy by altering the IgE profile. However, due to the high rate of allergic reactions and the

risk of anaphylaxis, OIT should only be used under the supervision of clinicians and caregivers (32). Oral immunotherapy appears to be an effective technique of creating short-term tolerance to food allergens, according to current studies on cow's milk, hen's egg, peanuts, and wheat allergies (33, 34). However, whether OIT is successful in causing long-term tolerance to oral allergens is unknown. Because the tolerance generated by desensitizing therapy appears to be temporary, a long-term maintenance treatment is required to achieve a long-term benefit (35). There is evidence that desensitization can last for a long time after therapy is stopped, or even longer with a daily maintenance dosage (36, 37). The duration of the up-dosing phase, maintenance phase, OIT dosing, and adding omalizumab differ between therapeutic protocols, attempting to make these studies difficult to compare (38). The most major constraint in OIT's usage in everyday clinical practice has been its safety. Many trials combine oral immunotherapy with anti-IgE treatment to increase safety and efficacy. To accurately measure the long-term effects, the influence on quality of life, and the cost-effectiveness of oral immunotherapy, further high-quality RCTs are needed (39). Inuo et al. released the findings of a single-center, double-blind RCT in 2018 to assess the effectiveness and safety of immunotherapy with hydrolyzed formula in children allergic to cow's milk protein (33). The research included twenty-five individuals ranging in age from one to nine years of age. For the first eight weeks, all participants were given a partially hydrolyzed formula (pHF); after that, the children were divided into two groups: pHF and extensively hydrolyzed formula (eHF). The OIT lasted for 16 weeks in total. A total of 60 mL of cow's milk was used in a DBPCFC (double-blind placebo-controlled food challenge) before and after the treatment. Both groups consumed 20 mL pHF or eHF daily for the first 8 weeks, and then both groups consumed 20 mL pHF daily for the next 8 weeks. In DBPCFC, the endpoint was defined as a rise in the cow's milk protein threshold. There were substantial reductions in particular IgE levels in both groups; and threshold allergen levels in children with severe allergies in the partly hydrolyzed formula group. In the group with an extensively hydrolyzed formula, it grew greatly compared to the start of the investigation, but did not alter. The effectiveness of both formulations was similar, however the partially hydrolyzed formula was safer than the fully hydrolyzed formula. From the time they are born, children with CMA have had a significant impact on their eating and social lives. Despite the fact that many children with CMA have spontaneous remission, many doctors struggle to decide which cases to treat and when they should be treated, especially when considering the risks and advantages of CM-based OIT. Long-term and severe CMA patients may be eligible for OIT. As a result, an objective indication for both the prognosis and severity of CMA is required (40). The clinical signs of WA might vary depending on the allergen exposure route. Wheat intake is frequently the cause of typical IgE-mediated responses, with symptoms appearing within 2 hours after ingestion (41), after consuming wheat proteins, urticaria, angioedema, bronchial obstruction, nausea, stomach discomfort, or systemic anaphylaxis might ensue (42). Despite the fact that WA is quite common in children, little is known about its natural history. IgE-mediated WA in children has a typically good prognosis, with 45–69% of children becoming tolerant by the age of six (43-45). Keet et al. discovered that the median age at resolution was roughly 6-12 years in a large sample of wheat allergy individuals. By the age of four, 29 percent of children had developed tolerance, and by the age of ten, 62 percent had

developed tolerance. Thirty-five percent of those who were allergic as children were still allergic as teenagers (46). A recent retrospective cohort research in Japan looked at the variables linked to chronic WA. A total of 83 children with a history of an immediate-type allergic response to wheat were included in the study and observed until they were six years old. At 3, 5, and 6 years of age, the rates of tolerance acquisition, as measured by the OFC technique, were 20.5 %, 54.2 %, and 66.3 %, respectively. Patients who had an allergic reaction to all foods and wheat before the age of three and patients with a high level of wheat- or -5 gliadin-specific IgE antibodies were at a greater risk of developing chronic WA (45). Wheat intolerance occurs in 76–96% of people between the ages of 16 and 18 (47, 48). Cross-reactivity between grass pollen and wheat, on the other hand, is likely connected to certain panallergenes. CCD, Phl p 12, and profilin (49), cause an elevated incidence of wheat sensitivity in children, but not of WA sensitization (50). Dietary avoidance is the current treatment for WA, while OIT has recently been recommended for WA, with encouraging results. Only a few research studies have looked at the effectiveness and safety of OIT for WA [4, 65–68]. To develop tolerance in wheat-allergic youngsters, more research is needed to determine the optimum wheat OIT approach. WA is a frequent allergy in children, and depending on the route of allergen exposure, it can cause a variety of clinical symptoms.

4- CONCLUSION

In children with IgE-mediated wheat allergy, the prognosis is typically good. Component resolved diagnosis (CRD) may be effective in predicting the occurrence of persistent WA. Patients are now managed with dietary avoidance, although oral immunotherapy for wheat allergy has recently been proposed, with encouraging results. Despite this, more research is still needed to determine the optimum strategy for promoting tolerance in wheat/milk-allergic children. Clinicians and fundamental science researchers should collaborate to better understand the immunological features of patients and the changes induced by therapy, so that safer and more successful treatment approaches may be developed.

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