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To cite this article: P Pacharn & P Vichyanond (2017): Immunotherapy for IgE-mediated wheat allergy, Human Vaccines & Immunotherapeutics, DOI: [10.1080/21645515.2017.1356499](https://doi.org/10.1080/21645515.2017.1356499)

To link to this article: <http://dx.doi.org/10.1080/21645515.2017.1356499>



Accepted author version posted online: 12 Sep 2017.



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Abstract

Among various routes of immunotherapy for food allergy, oral immunotherapy (OIT) appears to have a promising result due to its ability to modify abnormal immunologic mechanism of IgE-mediated food allergy. Other methods for immunomodulation such as sublingual (SLIT) or epicutaneous (EPIT) immunotherapy which carry lower rates of systemic reactions, may have less efficacy. Wheat has recently been recognized as a more common cause of food-induced anaphylaxis than previously recognized, especially among young children, around the world. In wheat allergic patients, avoidance recommended as standard recommendation is not easy to follow, because wheat has been used as a common constituents in various kinds of consumed foods in every day's life. Therefore, wheat OIT may be considered as an alternative treatments for those in which wheat avoidance is not sufficient to avert frequent events of anaphylaxis resulting from inadvertent exposure to small amount of wheat among this population. Currently, only few clinical trials about wheat OIT are available. In this review, we discuss available protocols of wheat OIT, initial starting dose, maintenance dose, and the strategies to minimize the side effects during the treatment.

Keywords

Wheat, IgE-mediated, immunotherapy, oral immunotherapy

Wheat allergy

Wheat (*Triticum aestivum*) is one of the food products widely consumed worldwide. Wheat-related allergic disorders can be classified into autoimmune, allergic, or not autoimmune/not allergic conditions (1). In IgE-mediated wheat allergy, patients tend to have severe anaphylactic reactions when compared to reactions from other kinds of food such as cow milk and eggs (2). The epidemiologic study of IgE-mediated wheat allergy among 91 Thai children indicated that about half of these patients had history of serious anaphylaxis (3). In Asia, wheat is not only one of the most common causes of food-induced anaphylaxis (4, 5), but also of food-dependent, exercise-induced anaphylaxis (6).

Wheat proteins can be categorized into 4 fractions on the basis of their solubility, including albumin, globulin, gliadin, and glutenin. Among these proteins, omega5 gliadin showed the highest specificity to diagnose IgE-mediated wheat allergy, especially in children who have the history of anaphylaxis (7). However, wheat allergic children were also have positive IgE response to glutenins, alpha-, beta-, gamma-gliadins, and alpha amylase inhibitors (8). Therefore, the major allergens of IgE-mediated wheat allergy might be different depends on ethnicity and subtypes of population. Further studies are needed to identify the specific group of patients.

The natural history of IgE-mediated wheat allergy has been infrequently studied and reported. A large retrospective study from the United States reported the median age of resolution is 79 months, and approximately 35% of patients, wheat allergy persisted into adolescence (9). A recent prospective study in Thai children showed a similar median age of resolution of 6.3 years (76 months) (10). There were only few reports about wheat allergy in adults. The largest study was performed in 37 adults who had history of wheat allergy in Italy and Denmark (11). However, only 48% of cases had positive result for oral food challenge. In addition, they did not report the age of wheat allergy onset. The adult onset wheat allergy was reported in 6 Korean adults (12). All of them had history of anaphylaxis, and half of them related to exercise. Recently, an increase incidence of wheat-dependent, exercise-induced anaphylaxis after using hydrolyzed wheat protein

(HWP) containing soap was reported (13). Nevertheless, the relationship of HWP and adult onset wheat allergy is not clearly defined.

The standard of care of food allergy is strict avoidance to the incriminated food and prompt treatment of reactions from accidental exposure. However, wheat avoidance cannot to be strictly adhered to in real life situation. Wheat is used widely as constituents of various foods such as cakes, noodles, and also in seasoning soy sauce. Because of difficulty in completely avoidance, severe reactions on exposure and the late outgrowing of symptoms in wheat anaphylaxis, the need for alternative specific treatment is needed. Among these new strategies for food allergy treatment, oral immunotherapy (OIT) has been most studied.

Oral immunotherapy (OIT) to food allergens

OIT can induce oral tolerance to allergenic foods through modification of both innate and adaptive immune mechanisms. The immunological changes that were found in patients who underwent food OIT included decreased mast cell and basophil release of mediators of inflammation (14), increased food-specific IgG4, initial increase and later decrease in food-specific IgE (15) and expansion and affinity maturation of specific memory B cell (16). Among these mechanisms, inducible regulatory T cell stimulation and therefore release of IL-10 and IFN- γ plays a central role for tolerance induction.

OIT protocol

The standard OIT protocols consist of 3 phases. First, the initial escalation phase or rush phase in which food is given for 6-8 doses per day. It is usually started with a very small dose (initial dose commonly identified as eliciting dose from double-blind, placebo-controlled food challenge), then doses are increased the amount rapidly. This phase is generally performed in hospital since it carries a high risk of systemic reaction. At the end of this phase, a safety starting dose for home administration is identified. A build-up phase during which the amount of food is increased every 1-2 weeks (generally at 20-30 percent increment/visit) until the patients reaches the maintenance dose, generally at one serving dose which is

maintained for several years. In most studies, the efficacy of treatments is evaluated in terms of desensitization, and tolerance (sustained unresponsiveness). Desensitization denotes a condition in which patients are able tolerate maintenance dose during which no interruption of doses is occurred whereas sustained unresponsiveness denotes ability to tolerate doses even when patients discontinue doses. The desensitization is checked after 1 to 3 years of OIT. Oral food challenge test is performed while on treatment to determine desensitization. To establish sustained unresponsiveness (tolerance) patients stop taking doses of allergenic food for at least 2 weeks prior to performing another oral food challenge.

Protocols of wheat OIT among various reported studies varied widely in the initial dose, the maintenance dose, the study schedule, and the selection of study subjects. Further studies are still needed to identify protocol which is the most effective and produces the least adverse reactions.

Clinical trials

Comparing to the other common allergenic food such as milk, egg, or peanut, only few clinical trials about wheat OIT exist. Each study used various kinds of wheat products such as pasta, udon, and bread. However, the therapeutic results depend on the dose of wheat rather than the type of wheat products Nucera et al first reported a successful desensitized protocol in a girl with IgE-mediated wheat allergy. The patient tolerated 49 g of pasta, three times daily after 215 days of wheat OIT (17). However, the investigators could not demonstrate the immunological change after 6 months of treatment. Details on other clinical trials on wheat OIT are provided in Table 1. The largest cohort of wheat OIT were performed in 18 wheat anaphylaxis Japanese patients (18). After 2 years of treatment, the successful desensitization rate was 88.9%, but the tolerance decreased to 61.1% after two weeks of discontinuation of maintenance dose. Interestingly, Okada using 'very low dose', i.e., 2 grams of udon noodles (equivalent to 53 mg of wheat protein (WP)) once a week as a maintenance dose among young infants (about 2 years old) who were exquisitely sensitive to wheat (could not tolerate 15 grams of udon – equivalent to 400 mg of WP). After 1 years of treatment with this very low dose (53 mg of WP) with gradual home increase, the desensitization rate to 15 grams of udon noodles

was achieved in only 56% indicating that degree of desensitization and perhaps sustained unresponsiveness may be related to the amount of wheat that is used as maintenance dose (19).

Case reports of wheat OIT used protocols which varied widely. Most cases did not report the condition of tolerance, but all patient was desensitized. The failure case had not been reported. The lists of case reports show in Table 2.

Dose, frequency and duration

From the previous clinical trials and case reports, most studies use 5-6 grams of WP as a maintenance dose (18, 21-23). This approximates 2-3 of a piece of bread. The desensitization rate was obviously lower when the very low amount of the maintenance was used (19). Although, there is no study to compare rates and severity of the adverse reactions, severe reactions required adrenaline injection was only 0.04% by maintenance with 5.2 grams of WP (18). Interestingly, Rodriguez del Rio, et al indicated that their patients could also tolerate very high amount of maintenance dose of wheat (13 grams of WP) without systemic reactions (20). This could be due to lower degree of wheat sensitization among this group of patients inferring from higher eliciting dose of wheat during food challenges (2 grams, i.e., 2000 mg). Until now, there is no dose-ranging study in oral immunotherapy, but a dose-response relationship was observed in both subcutaneous (SCIT) and sublingual immunotherapy (SLIT) for respiratory allergens and insects (24). Therefore, this finding might apply to the OIT. For wheat OIT, the desensitization rate was higher when maintenance with 5.2 grams of WP compared to 400 mg of WP (88.9% VS 56%). However, the significant difference in clinical results was not observed from these studies of peanut OIT. Surprisingly, the rate of desensitization was 62% with maintenance dose of 800 mg peanut protein (25), compared to 93% with only 300 mg maintenance dose of peanut protein (26). In this study, the investigators continued to increase the amount of maintenance dose of peanut protein to 4,000 mg in the 5 years follow up period, after which about 50% of patients achieved sustained unresponsiveness (27). Therefore, the dose-ranging studies to each specific food are needed to find the most effective dose for individual group of patients.

Interestingly, frequency of maintenance phase in these studies varied from once daily to once a week. Recently, Takaoka et al reported the result comparing frequency between 2 times/week to 6 times/week of wheat ingestion (28). They found that the target dose reached was not different even when the frequency of wheat intake was reduced to twice a week, after 6 months of treatment. Further studies in a larger group of patients with a long term follow up is needed to confirm this finding.

The duration of successful OIT depends on the target wheat dose to be reached. In general, desensitization state were achieved within 6 months in both clinical trials and case reports. However, longer duration of maintenance may be required to reach sustained unresponsiveness. The longest follow up study in wheat OIT showed the tolerance rate was 61.1% after 2 years of maintenance (18). Therefore, a longer duration may needed to increase the rate of tolerance. A previous study of 2 years egg OIT showed low tolerance rate – 27.5% (29). However, with longer period of maintenance (to 4 years) the tolerance rate increased to 50% (30). However, it may not be necessary to maximize the tolerance rate, since desensitization could avert adverse reactions to small exposure to allergic foods and thus could bring about a significantly improved quality of life.

Safety concerns

The adverse reactions during OIT are common and can occur at any phases of the protocol. The numbers and severity of reactions depend on the protocol, degree of wheat sensitization of the patients, along with cofactors that could aggravate symptoms. The precipitating causes of adverse reactions during OIT were identified among patients who underwent peanut OIT (31). These were concurrent illnesses, suboptimal controlled asthma, administration on an empty stomach, physical exertion after dosing, and dosing during menstruation period. Sato, et al (18) reported 3 episodes of severe reactions requiring adrenaline injections during their long term build-up/maintenance. However, they could not identified any associating aggravating factors. Omalizumab and premedication have been used to reduce the symptoms during food OIT. The use of omalizumab 8-12 weeks prior to starting the OIT allowed patients to tolerate higher doses of food intake with

lower rates adverse reactions compared to the placebo treated group (32-34). There is no clinical trial about the use of omalizumab for wheat OIT. In our study, with omalizumab given only 3 weeks prior to increasing the dose of wheat was helpful in reaching higher build up dose (22).

Sublingual immunotherapy (SLIT) and epicutaneous immunotherapy (EPIT)

SLIT is another route of immunotherapy that have been studied for food immunotherapy. It used less amount of the allergens and also was associated with lower rate of adverse reactions comparing to OIT. In a double-blinded, placebo-controlled study comparing peanut SLIT and OIT, both were effective for increasing the threshold of peanut ingestions (35). However, the threshold was significantly greater in OIT group than to SLIT (141 VS 22 fold), however, adverse reactions were more frequent in the OIT group. Until now, there is no study was reported to use SLIT to wheat.

EPIT is an interesting new therapeutic option for food allergy. It can activate skin Langerhans cells by apply the allergen-containing patch to the skin. A study in mice showed that OIT, SLIT, and EPIT can induce different subset of regulatory T cell (36). Foxp3⁺ Tregs were induced with a greater number in EPIT. The suppressive activity of EPIT-induced Tregs did not depend on IL-10 but involved CTLA-4 whereas SLIT induced IL-10⁺ cells, and the activation depends on IL-10. For OIT, the activation was demonstrated through both mechanisms. They also showed that OIT or SLIT-induced Tregs, lost their suppressive activities after treatment was discontinued, whereas it was still effective 8 weeks after the end of treatment in EPIT. This finding suggested the induction of a longer tolerance can occur with EPIT. A pilot study in children with cow's milk allergy found that EPIT failed to demonstrate a statistically significant improvement with a cumulative total dose of milk ingestion after 3 months of treatment (37). However, the rates of adverse reactions were very low and limited to the skin. Most recently, Jones et al (38) reported the efficacy of peanut EPIT (peanut Viaskin) after 52 weeks of treatment. They divided patients into 3 groups i.e., placebo, Viaskin peanut 100µg (VP100), and Viaskin peanut 250µg (VP250). They demonstrated that patients who treated with Viaskin peanut could tolerate a 10-fold increase consumed dose (12%, 46%, and 48% in placebo,

VP100, and VP250). They also found that younger patients (between 4-11years) had a higher rate of successful treatment. Because the good safety profile in EPIT, future researches about EPIT wheat could be of very interesting direction for treatment of wheat allergy, especially in severe cases.

Expert opinion

Further clinical and immunological studies about wheat OIT are needed. At present, there is still no randomized, placebo-controlled study in wheat OIT. The duration of treatment and the amount of maintenance dose are inconclusive. The EPIT for wheat allergic patients is interesting, especially in wheat anaphylaxis patients.

Conclusion

Despite a variation in protocols for wheat OIT, all studies showed the effectiveness for inducing desensitization among wheat allergic patients. The tolerance rate is still low. Future researches to increase the tolerance rate, and to minimize the adverse events are needed. EPIT to wheat might reduce the risk of adverse events in severe allergic patients.

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Table 1 Clinical trials on wheat OIT

First author	Design	N	History of anaphylaxis	ED	MD	Duration	Outcome
Rodriguez del Rio (20) (2014)	Prospective, No control	6	4/6	2.12g of WP	13g of WP	6 m	Drop out 1
							DS 83%
Sato (18) (2015)	Prospective, Historical control	OIT 18 Control 11	18/18	0.08g of WP	5.2 g of WP	2 y	Drop out 2
							DS 88.9%
							SU 61.1% VS 9.1% in control
Okada (19) (2016)	Retrospective	57 (VL tolerance 32, VL reactive 25)	26/57 (46%) VL tolerance (10/32, 31%) VL reactive (16/25, 64%),	53 mg of WP	400 mg of WP	1 y	VL tolerance: DS 56%
							VL reactive: DS 0%

ED = Eliciting dose, MD = Maintenance dose, DS = desensitization, SU = sustained unresponsiveness, WP =

wheat protein, VL = very low maintenance dose

Table 2 Case reports in wheat OIT

First author	N	ED	Time to maintenance	MD	Adverse Events
Fujino A (21) (2010)	2	Not shown	8-10 days	5.6 g of WP	6-9 times (not describe severity)
Pacharn P (22) (2014)	2	30mg, 300mg of wheat flour	2-5 months	6-8 g of WP	Anaphylaxis 2-4 times during escalation phase
Vila L(23) (2015)	3	Not shown	10 weeks (Patient 3)	6.5 g of WP	Occasional abdominal pain, urticarial (related to exercise)

ED = Eliciting dose, MD = Maintenance dose