A practical focus on wheat oral immunotherapy

Stephanie Leeds, M.D.,[1] Ami Belmont, M.D.,[2] Holly Winfield, R.D.,[3] and Anna Nowak-Wegrzyn, M.D., Ph.D.[3,4]

ABSTRACT

Wheat is a dietary staple in many cultures as well as a common food allergen. Although not as extensively studied as other forms of oral immunotherapy, the current literature suggests that wheat oral immunotherapy (WOIT) can result in successful desensitization. There has only been one multicenter, double-blind, randomized controlled trial of WOIT, along with several open-label nonrandomized trials. The trials were limited by several factors, including small sample sizes; demographic skew; and heterogeneity in dosing, duration, and outcomes. The majority of WOIT regimens results in desensitization, with literature that indicates that a longer duration and higher dosing may lead to more clinical success. WOIT has been associated with adverse events, including allergic reactions, but these events seem to decrease over time. Study on WOIT is underway, but evidence from trials suggests it can be successful and safe. Further studies will need to optimize dosing protocols to improve efficacy and safety.

(J Food Allergy 4:136–143, 2022; doi: 10.2500/jfa.2022.4.220029)

BRIEF OVERVIEW OF WHEAT ORAL IMMOTHERAPY

Wheat is a common food allergen as well as a ubiquitous staple grain that is difficult to avoid in many modern diets. Wheat allergy is common in childhood, with most cases resolving by adulthood; however, there is a segment of the wheat allergy population that will have persistent wheat allergy over their lifetime.[1] In addition, wheat gliadin has been shown to have a broad range of *in vitro* cross-reactivity with other cereal grains, such as barley, rye, and oat, and there may be a subset of patients with wheat allergy who react to these grains as well (with rye having the highest rate of clinical cross-reactivity).

For those who have persistent wheat allergy, as well as those who prefer a proactive, interventional therapy for a variety of reasons, wheat oral immunotherapy (WOIT) may be a desirable option. WOIT is not as well studied as immunotherapy for other foods, such as milk, egg, and peanut. There is considerable heterogeneity among WOIT trial protocols, and published studies were often small, with a study population skewed toward school-aged patients.[2–7] Despite these limitations, results from these studies largely support that WOIT results in successful desensitization, with success likely related to both duration of treatment and dosing schedule, wherein longer time periods and higher maintenance dosing increases the likelihood of success.

DOSING SCHEDULES

WOIT trial protocols vary substantially. To date, there has been one randomized controlled trial (RCT),[2] as well as a handful of open-label trials, most nonrandomized.[3–7] The dosing regimens, types of wheat protein (WP) used, and outcomes studied are fairly diverse (Table 1).[2–7] The largest RCT was conducted over 2 years and consisted of 46 subjects, who were randomized to commercially prepared vital wheat gluten (VWG) product or placebo (with cross over to high-dose VWG).[2] Primary end points included double-blind placebo controlled food trials at the end of years 1 and 2 by using maximum doses of 4443 mg of WP (equivalent to 1–2 slices bread) and 7443 of WP (equivalent to 2–4 slices of bread), respectively.

At the end of year 1, 52% of the low-dose WOIT group (12/23) and 0% of the subjects who received placebo (0/23) achieved the successfully consumed dose (SCD) of 4443 mg ($p < 0.0001$), with median SCDs of

From the [1]Department of Pediatrics, Yale School of Medicine, New Haven, Connecticut; [2]Department of Medicine, Yale School of Medicine, New Haven, Connecticut; [3]Department of Pediatrics, NYU Grossman School of Medicine, Hassenfeld Children's Hospital, New York, New York; and [4]Department of Pediatrics, Gastroenterology and Nutrition, Collegium Medicum, University of Warmia and Mazury, Olsztyn, Poland

S. Leeds receives consultancy fees from Regeneron. A. Nowak-Wegrzyn receives research support from the National Institute of Allergy and Infectious Diseases, DBV Technologies, Astellas Pharma, Danone, and Nestle, and consultancy fees from Regeneron, Nutricia, and Gerber Institute. The remaining authors have no conflicts of interest to disclose pertaining to this article

No external funding sources reported

Address correspondence to Anna Nowak-Wegrzyn, M.D., Pediatric Allergy and Immunology, NYU Grossman School of Medicine, Hassenfeld Children's Hospital, 160 East 32nd St., LM3, New York, NY 10016

E-mail address: Anna.nowak-wegrzyn@nyulangone.org

*This manuscript is part of the **Journal of Food Allergy** collection of published works referred to as the "Oral Immunotherapy Manual." The contents of this work reflects the opinion(s) of the author(s) and is not intended to replace published guidelines or the clinician's medical advice in the doctor-patient relationship*

Table 1 **Overview of selected wheat OIT trials**

Study, y; Country	Design	Subjects	Form of Wheat Used	Dosing	Primary Outcome and/or Efficacy	Immunologic Changes	Adverse Effects	SU
Nowak-Wegrzyn *et al.*,[2] 2019; United States	Multicenter, double-blind, randomized, placebo controlled trial	Patients were randomized 1:1; *n*= 23 (median age 8.7 y; 78% boys) on low-dose OIT; *n* = 23 (median age 8.6 y, 78% boys) on placebo; the patients on placebo were then crossed-over to high-dose OIT after 1 y	Irradiated raw VWG; cornstarch for placebo	Maintenance dose of 1445 mg of WP (low dose) or 2748 mg of WP (high dose) for 8 wk to 1 y	52.2% of patients on low dose and 0% of patients on placebo tolerated > 4443 mg of WP after 1 y; 30.4% of patients on low dose tolerated 7443 mg after 2 y; 57.1% of patients on high dose cross-over tolerated 7443 mg after 1 y	No significant change in wheat or component IgE value; increased wheat and omega-5 gliadin IgG_4 in OIT group	15.4% of the low-dose OIT doses led to an adverse reaction; 0.08% of doses led to reactions treated with IM epi	After 8–10 wk off therapy, 13% had SU
Sato *et al.*,[3] 2015; Japan	Open-label, non-randomized, historically controlled trial	*n* = 18 (median age, 9.0 y; 61% boys) on OIT; *n* = 11 (median age, 7.0 y) as a historical control group	Boiled udon noodles	Initial inpatient rush build up; maintenance dose of 5.2 g of WP for >3 mo	61% of patients on OIT tolerated a total of 1.3 g of WP 2 wk after stopping OIT compared with 9% of historical controls	Decreased wheat-specific IgE at 2 y	26.4% of inpatient doses and 6.8% of outpatient doses had adverse reactions; 0.02% of total doses required treatment with IM epi	After 2 wk off therapy, 61% had SU to 1.3 g of WP
Nagakura *et al.*,[4] 2020; Japan	Open-label, non-randomized, historically controlled trial	*n* = 16 (median age, 6.7 y) on low-dose OIT; *n* = 11 (median age, 6.4 y) as a historical control group	Boiled udon noodles	Initial inpatient rush buildup; maintenance dose of 53 mg of WP for 1 y	68.8% of patients on OIT tolerated 53 mg of WP 2 wk after stopping OIT; 25% could tolerate 400 mg; 9.1% and 0.0% of control patients could tolerate each dose, respectively	Decreased wheat and omega-5 gliadin IgE levels at 1 y; increased wheat and omega-5 gliadin IgG and IgG_4 at 1 mo	32.1% of inpatient doses and 4.1% of home doses had adverse reactions; 5 patients had 7 episodes of anaphylaxis, none needed IM epi	After 2 wk off therapy, 68.8% had SU to 53 mg of WP and 25.0% had SU to 400 mg

Table 1 **Continued**

Study, y; Country	Design	Subjects	Form of Wheat Used	Dosing	Primary Outcome and/or Efficacy	Immunologic Changes	Adverse Effects	SU
Sugiura *et al.*,[5] 2020; Japan	Open-label, nonrandomized controlled trial	Groups were assigned by patient preference; $n = 35$ (median age, 5 y) on low-dose OIT; $n = 10$ (median age, 6 y) in the control group	Boiled udon or somen noodles	Individualized dosing aiming for a maintenance dose 10 time greater than maximal tolerated dose at baseline	37.5% of the patients on OIT passed a low-dose OFC (226 mg of WP) after 1 y of treatment compared with 10% of the control patients	Decreased wheat and omega-5 gliadin IgE after 12–15 mo	59/9175 (0.64%) doses resulted in adverse events, none required IM epi or ED visit	SU not assessed
Kulmala *et al.*,[6] 2018; Finland	Multicenter, open-label, nonrandomized, uncontrolled trial	$N = 100$ (mean age, 11.6 y; 67% boys) were given OIT	Boiled spaghetti noodles	Maintenance dose of 2 g of WP for 3 mo, followed by unrestricted daily wheat for 9 mo	57% of patients completed the protocol and reported being able to tolerate wheat in their daily diet after 16 mo	Decreased wheat, gluten, and omega-5-gliadin IgE after 1 y	94% of patients experienced reactions during the study; 11 patients used 12 doses of IM epi	SU not assessed
Ogura *et al.*,[7] 2020; Japan	Multicenter, open-label, randomized, uncontrolled trial	Patients were randomized 1:1; $n = 12$ (median age, 5.5; 67% boys) on low-dose OIT; $n = 12$ (median age, 5.0 y; 67% boys) on high-dose wheat OIT	Boiled pasta, boiled udon, or bread	Maintenance dose of 650 mg (low dose) and 2.6 g (high dose) of WP	At 1 y, 17% and 50% of the low- and high-dose OIT groups, respectively, passed OFC; at 2 y, 58% of both groups passed OFC	Decreased wheat IgE after 1 y in both groups and decreased omega-5-gliadin IgE in the low-dose group; no changes to wheat or omega-5-gliadin IgG and IgG_4	Lower rate of reaction in low-dose OIT (4.76% of doses) compared with high-dose OIT (8.82% of doses)	At 1 y, after 2 wk off therapy, 17% and 50% of the low- and high-dose OIT groups, respectively, had SU; at 2 y, 58% of both groups had SU

ED = emergency department; epi = epinephrine; IgE = immunoglobulin E; IM = intramuscular; OFC = oral food challenge; OIT = Oral immunotherapy; SU = sustained unresponsiveness; VWG = vital wheat gluten; WP = wheat protein.

Table 2 **Wheat oral immunotherapy dosing schedule with vital wheat gluten*#**

Dose No.	Dose of WP, mg	Dose of Wheat Powder, mg	Interval	Dose Format§	% Increase
1	0.07	0.1	Day 1	Vial	100
2	0.14	0.2	Day 1	Vial	100
3	0.28	0.4	Day 1	Vial	100
4	0.57	0.8	Day 1	Vial	100
5	1.1	1.5	Day 1	Vial	87.5
6	2.1	3.0	Day 1	Vial	100
7	4.3	6.0	Day 1	Vial	100
8	**8.5**	**12.0**	**Day 1**	**Vial**	**100**
9	17.8	25	2 wk	Vial	108
10	35.5	50	2 wk	Vial	100
11	53.3	75	2 wk	Capsule	50
12	71	100	2 wk	Capsule	33
13	111	156	2 wk	Capsule	56
14	160	225	2 wk	Capsule	44
15	213	300	2 wk	Capsule	33
16	284	400	2 wk	Capsule	33
17	**373****	**525**	**2 wk**	**Scoop 1**	31
18	476	670	2 wk	Scoop 2	28
19	596	840	2 wk	Scoop 3	25
20	731	1030	2 wk	Scoop 4	23
21	923	1300	2 wk	Scoop 5	26
22	1150	1620	2 wk	Scoop 6	25
23	**1445##**	**2035**	**2 wk**	**Scoop 7**	26
24	1800	2535	2 wk	Scoop 8	25
25	2272	3200	2 wk	Scoop 9	26
26	**2748$$**	**3870**	**2 wk**	**Scoop 10**	21

WP = Wheat protein.
**From Ref. 2.*
#Vital wheat gluten powder contains ~71% of WP.
§All scoops are approximate weights based on scoop size and leveling.
¶Dose escalation occurs in a clinical research center.
||8.5 mg of WP is the maximum dose escalation on day 1.
***373 mg of WP is the minimum maintenance dose.*
##1445 mg of WP is the maximum dose escalation for the participants initially on active treatment.
§§2748 mg of WP is the maximum dose escalation for placebo cross-over participants.

4443 mg versus 143 mg at the start of the trial. At year 2, 30% of the low-dose group (7/23) achieved the SCD of 7443 mg of WP in contrast to 57% of the high-dose cross-over group (12/21). The low-dose group had a second challenge 8–10 weeks off therapy, with 13% of the subjects (3/23) showing sustained unresponsiveness. In terms of tolerability of the study regimen, it is noteworthy that 82% of the subjects in the low-dose WOIT group achieved the maintenance dose after 1 year, whereas, in the high-dose cross-over group, 57% achieved the maintenance dose. In terms of safety, the dosing regimen used in this study was not found to be associated with more adverse events compared with oral immunotherapy (OIT) for other foods.

As shown in Table 1, studies used a wide variety of dosing regimens, with a large WP range, of 53 mg (1% WP in a single slice of bread) to 5200 mg (2–3 slices of bread).[2–7] Although some studies used a standardized initial dose, others used initial doses based on either the threshold dose in the oral food challenge (OFC), severity of symptoms, or both.[2–7] Updosing regimens varied substantially as well, with two studies that performed an initial inpatient rush buildup over 5 days,[3,4] whereas other studies relied on slower up-titration either in the clinic or at home every 2–4 weeks or by using symptoms to guide dose increases.[2,5–7] Most study protocols involved dosing suspension for illness, and a rest period without exercise or bathing for 1–2 hours after dosing.

Table 3 **Alternative wheat OIT dosing schedule using commercial foods*#**

Dose No.	Dose of WP, mg	Dose of Orzo Pasta, no. whole cooked orzo grains§	Alternatives (closest dose approximation)	Interval	% Increase
1	2.6 mg	1/2	—	Day 1	100
2	**5.2 mg**	1	—	Day 1	100
3	10.4	2	—	2 wk	100
4	20.8	4	—	2 wk	100
5	41.6	8	—	2 wk	100
6	52.0	10	—	2 wk	25
7	62.4	12	—	2 wk	20
8	83.2	16 (1/4 tsp)	—	2 wk	33
9	114.4	22 (1/3 tsp)	1 oyster cracker¶	2 wk	37.5
10	166.4	32 (1/2 tsp)	—	2 wk	45.5
11	249.6	48 (3/4 tsp)	—	2 wk	50
12	332.8	64 (1 tsp)	3 oyster crackers	2 wk	33.3
13	416	80 (1 tsp and 1/4 tsp)	2 saltine crackers‖ or 4 oyster crackers	2 wk	25
14	582.4	96 (1 tsp and 1/2 tsp)	3 saltine crackers or 6 oyster crackers	2 wk	40
15	665.6	128 (2 tsp)	7 oyster crackers	2 wk	14.3
16	800	154 (2 tsp and 1/3 tsp and 4 grains)	4 saltine crackers or 8 oyster crackers	2 wk	20
17	998.4	192 (3 tsp [1 tbsp])	5 saltine crackers or 10 oyster crackers	2 wk	24.8
18	1331.3	4 tsp (leveled)	6 saltine crackers or 13 oyster crackers	2 wk	33.3
19	1664	5 tsp (leveled)	8 saltine crackers or 16 oyster crackers	2 wk	25
20	**1996.8**	**6 tsp (= 2 tbsp = 1 oz) (leveled)**	**10 saltine crackers or 20 oyster crackers or one slice of white bread****	2 wk	20

OIT = Oral immunotherapy; WP = wheat protein.

**The dosing schedule has not been validated in clinical trials; it is based on the conversion from the vital wheat gluten research dosing protocol in Table 2 to dosing by using commercial wheat products. Dosing should be adjusted and/or individualized based on the patient's test results, past reactions, and adverse events during desensitization.*

#These are commercially available foods that might be suitable for the purpose of wheat OIT. The protein estimates and proposed doses are based on the nutritional information on the product label provided by the manufacturer. Important! The protein content might vary from batch to batch. When switching among different foods, caution is recommended because the equivalents of WP are approximate. Transition from one product to another should be done under a physician's supervision in a controlled setting. The product label should always be inspected for changes in the nutritional information and/or protein content that can be introduced without obvious changes in the packaging.

§Barilla orzo wheat pasta (Barilla G. e R. Fratelli S.p.A, Parma, Italy), 1 oz. dry pasta = 10.5 tsp cooked pasta, which contains ~3500 mg of WP.

¶Schnucks oyster crackers (Schnuck Markets, Inc St., Louis, MO); 1 oyster cracker contains ~100 mg of WP.

‖Nabisco Premium Saltine cracker (East Hanover, New Jersey); one serving= 5 crackers contain ~1000 mg of WP; 1 cracker contains 200 mg of WP.

***Wonder Classic White Bread (Flowers Foods, Inc., Thomasville, GA); serving size = 2.00 slices (57 g) contains ~4000 mg of WP; 1 slice = 2000 mg of WP.*

A research protocol based on the study by Nowak-Wegrzyn *et al.*[2] is shown in Table 2. A comparable protocol based on the commercially available wheat products is presented in Table 3. These are commercially available foods that might be suitable for the purpose of WOIT. The protein estimates and proposed doses are based on the nutritional information on the product label provided by the manufacturer. Protein content might vary from batch to batch. When switching between different foods, caution is recommended because the equivalents of WP are approximate. Transition from one product to another should be done under a physician's supervision in a controlled setting. The product label should always be inspected for changes in the nutritional information and protein content that can be introduced without obvious changes in the packaging.

DOSE OPTIONS, PREPARATION, AND MASKING

There exists a plethora of different wheat products that can be used in WOIT, including VWG, wheat

Table 4 **Potential commercial food alternatives for wheat oral immunotherapy***

Wheat Product	Brand	Estimated WP Content (1 serving)#	Benefits	Challenges
Vital wheat gluten	Arrowhead Mills (Chicago IL) vital wheat gluten	6000 mg in a 9-g single serving; 3000 mg = in 4.5 g serving	Precise dosing, concentrated, masked easily	Less appealing in higher doses
Pasta	De Cecco (New York City, NY) no. 12 spaghetti	3000 mg; 1/2 cup cooked pasta or ~20 noodles	More appealing, easy to obtain	Less precise, cook time may alter protein content
	Barilla (Northbrook, IL) orzo wheat pasta	1 oz of dry pasta = 10.5 tsp of cooked pasta, which contains ~3500 mg of WP	More appealing, easy to obtain	Less precise, cook time may alter protein content
Bread	Nature's Own (Thomasville, GA) 100% whole wheat bread	4443 mg of WP (1–2 slices); 1 slice = 3000 mg	More appealing, easy to obtain	Less precise
	Wonder (Thomasville, GA) classic white bread	Serving size = 2.00 slices (57 g), which contains ~4000 mg of WP; 1 slice = 2000 mg of WP	More appealing, easy to obtain	Less precise
Crackers	Ritz Crackers (Chicago, IL)	3000 mg in 12 crackers	More appealing, easy to obtain and split	Less precise
	Schnucks (Louis, Mo) oyster crackers	1 oyster cracker contains ~100 mg of WP	More appealing, easy to obtain	Less precise
	Nabisco (East Hanover, NJ) premium saltine crackers	1 serving = 5 crackers contain ~1000 mg of WP; 1 cracker contains 200 mg of WP	More appealing, easy to obtain	Less precise
Udon noodles	Annie Chun's (La Palma, CA) fully cooked udon noodles	7000 mg in a 170-g single serving (1 pack); 3000 mg in an ~73-g serving size (<1 pack)	More appealing	Less precise, cook time may alter protein content; may need a gram scale to get precise dosing
Wheat flour	Arrowhead Mills white flour (barley free)	3000 mg in 3 tbsp of cooked wheat flour	Easy to obtain	Requires larger volume, difficult to mask, must be cooked for food safety concerns

WP = Wheat protein.

**These are commercially available foods that might be suitable for the purpose of wheat oral immunotherapy. The protein estimates and proposed doses are based on the nutritional information on the product label provided by the manufacturer. Important! The protein content might vary from batch to batch. When switching among different foods, caution is recommended because the equivalents of WP are approximate.*

#*Estimated WP content is based on the information provided by the manufacturer.*

flour, and foods that contain wheat (*e.g.*, bread, pasta, udon noodles), and partially hydrolyzed WP (Table 4). The use of wheat food items, *e.g.*, pasta, may be more appealing and allow for improved adherence, measuring dose amounts can be less precise. These products may have variable amounts of WP, and factors, *e.g.*, cooking time, can alter the WP content. Purified products, *e.g.*, VWG, tend to be more concentrated, which allows dose delivery in a smaller volume, which is more conducive to mixing. Wheat flour contains less WP, thus higher and poorly tolerated quantities may be required. VWG seems to be the most ideal dosing form for standardization, precision, and ease of masking, and it can be obtained commercially and mixed with any food. VWG may be especially useful during the initial stages of WOIT when low doses are being administered. However, once higher doses or maintenance doses of WP are reached, switching to wheat products such as pasta, bread, or crackers may be a preferred option for some patients on long-term WOIT.

SPECIFIC CHALLENGES AND CONSIDERATIONS

Patient Selection

Ideally, risk stratification of patients before initiation of WOIT could help guide individualized discussion about likely outcomes of therapy. Unfortunately, there currently are no reliable, predictive biomarkers for this purpose. One study suggests that baseline specific immunoglobulin E (IgE) to omega-5 gliadin might be

correlated with efficacy and safety of WOIT because the study participants with a higher baseline omega-5 gliadin-specific IgE were less likely to reach maintenance dosing.[6] Basophil activation tests and T-cell phenotyping are also being studied as biomarkers in food immunotherapy trials, but no single biomarker has been able to reproducibly predict prognosis during WOIT as of yet.[8] Given the inability to risk stratify, all patients interested in WOIT should have counseling with regard to therapy goals, current hardship of avoidance, logistical burden of treatment, and potential adverse effects.

Safety

Patient selection is critical; patients should have confirmed allergy, absence of specific comorbid diseases, including eosinophilic gastrointestinal disease and uncontrolled asthma, and an understanding of therapy limitations with a clear motivation and commitment to adhere to office visits and dosing schedules. However, even with rigorous attention to patient selection and shared medical decision-making, all patients on WOIT should be counseled with regard to the risk of reactions during dosing. Published studies reported reactions associated with various WOIT protocols, ranging from ~4% to 30% of doses (see Table 1).[2–7] Reactions were generally mild or moderate, with low rates of epinephrine administration. Reactions were also more common with high-dose OIT compared with low-dose OIT, and they tended to decrease over time. Patients should also be counseled with regard to the risk of eosinophilic gastrointestinal disease associated with OIT, which publications report ranges from 2.7% to 30% of trial subjects who received treatment for various foods.[9,10]

Cofactors for Allergic Adverse Events

The most considerable cofactors associated with reactions to any form of OIT include dosing on an empty stomach as well as dosing associated with exercise, hot showers, menses, sleep deprivation, and concomitant use of nonsteroidal anti-inflammatory drugs. However, particular attention should be paid to exercise as a risk factor in WOIT, given the phenomenon of wheat-dependent exercise-induced anaphylaxis. In one study with 25 patients undergoing rush WOIT, exercise-provocation tests (EPT) were performed after the ingestion of a full-dose wheat product.[11] Fourteen patients (66.7%) were diagnosed with having exercise-induced allergic reactions while on desensitization (EIARD), which remained 5 years after rush OIT in 11 patients (52.4%). Case reports also support the phenomenon of exercise-induced reactions in the setting of WOIT, including during maintenance.[12,13] Another retrospective chart review looked specifically at EPTs in patients deemed high risk for EIARD after successful desensitization to 5200 mg WP and found that 48% (15/31) developed reactions. Neither clinical characteristics nor IgE levels predicted reactions. Interestingly, among the patients who were positive for EIARD and who underwent a second EPT, the EIARD disappeared in four of six participants.[14] Also, a retrospective study conducted in Japan showed that, after WOIT, 25% of the subjects (6/24) had a positive EPT result; one subject required treatment with epinephrine.[15] Taken together, results of these studies suggest that consideration of an EPT before liberalizing exercise restrictions may be important for patients undergoing WOIT.

Adjunct Therapies

In efforts to improve WOIT outcomes, some investigators are looking at adjunct therapies. One study compared three groups of children receiving slow, low-dose OIT with egg, milk, and wheat by classifying the subjects as those who did not use antihistamines or leukotriene antagonists, those who used them temporarily during OIT, and those who used them continuously during OIT.[5] The three groups did not differ in the percentage of doses that led to adverse events, the percentage of subjects who achieved the maintenance dose, and the percentage of subjects who passed the final OFC. This study did not randomize patients and did not analyze outcomes based on specific foods; as such, although this study does not support routine prescription of these medications, an effect on WOIT adverse events and success rates cannot be ruled out. Studies are also underway that look at biologics in conjunction with food OIT, but little has been systematically studied with regard to the combination of biologic therapy with WOIT.

Office Set up and Staffing

To maximize the likelihood of safe and effective OIT outcomes, medical practices need to ensure that they have sufficient staffing, space, scheduling, and support.[16]

CONCLUSION AND FUTURE DIRECTIONS

Beyond the published studies reviewed here, investigator-initiated clinical trials are ongoing and will likely determine the optimal dosing protocol and maintenance dose of WOIT performed with intact proteins. Based on current publications, WOIT efficacy is likely related both to the dose and the duration of treatment, and higher dosing may be limited by adverse effects, particularly with more allergenic protein sources such as VWG. It is clear that future research will be needed to further investigate optimal WOIT dosing, mode, duration, and outcomes, with trials recruiting more heterogeneous and representative patient populations.

CLINICAL PEARLS

- There are limited data to date on WOIT, with one RCT and considerable heterogeneity among studies, but analysis of current data suggests that WOIT can be effective and safe.
- The efficacy of WOIT seems likely related to dosing schedules and duration, with higher dosing and longer duration of treatment leading to more success; however, higher dosing is limited by more adverse effects.
- Further studies, including more RCTs, are needed to develop and hone safe and effective WOIT protocols.

ACKNOWLEDGMENT

Thanking Marion Groetch, RD for her contribution to this chapter.

REFERENCES

1. Keet CA, Matsui EC, Dhillon G, et al. The natural history of wheat allergy. Ann Allergy Asthma Immunol. 2009; 102:410–415.
2. Nowak-Weôgrzyn A, Wood RA, Nadeau KC, et al. Multicenter, randomized, double-blind, placebo-controlled clinical trial of vital wheat gluten oral immunotherapy. J Allergy Clin Immunol. 2019; 143:651–661.e9.
3. Sato S, Utsunomiya T, Imai T, et al. Wheat oral immunotherapy for wheat-induced anaphylaxis. J Allergy Clin Immunol. 2015; 136:1131–1133.e7.
4. Nagakura K-I, Yanagida N, Sato S, et al. Low-dose-oral immunotherapy for children with wheat-induced anaphylaxis. Pediatr Allergy Immunol. 2020; 31:371–379.
5. Sugiura S, Kitamura K, Makino A, et al. Slow low-dose oral immunotherapy: threshold and immunological change. Allergol Int. 2020; 69:601–609.
6. Kulmala P, Pelkonen AS, Kuitunen M, et al. Wheat oral immunotherapy was moderately successful but was associated with very frequent adverse events in children aged 6-18 years. Acta Paediatr. 2018; 107:861–870.
7. Ogura K, Yanagida N, Sato S, et al. Evaluation of oral immunotherapy efficacy and safety by maintenance dose dependency: a multicenter randomized study. World Allergy Organ J. 2020; 13:100463.
8. Hardy LC, Smeekens JM, Kulis MD. Biomarkers in food allergy immunotherapy. Curr Allergy Asthma Rep. 2019; 19:61.
9. Lucendo AJ, Arias A, Tenias JM. Relation between eosinophilic esophagitis and oral immunotherapy for food allergy: a systematic review with meta-analysis. Ann Allergy Asthma Immunol. 2014; 113:624–629.
10. Petroni D, Spergel JM. Eosinophilic esophagitis and symptoms possibly related to eosinophilic esophagitis in oral immunotherapy. Ann Allergy Asthma Immunol. 2018; 120:237–240.e4.
11. Furuta T, Tanaka K, Tagami K, et al. Exercise-induced allergic reactions on desensitization to wheat after rush oral immunotherapy. Allergy. 2020; 75:1414–1422.
12. Kusunoki T, Mukaida K, Hayashi A, et al. A case of wheat-dependent exercise-induced anaphylaxis after specific oral immunotherapy. J Investig Allergol Clin Immunol. 2014; 24:358–359.
13. Calvani M, Sopo SM. Exercise-induced anaphylaxis caused by wheat during specific oral tolerance induction. Ann Allergy Asthma Immunol. 2007; 98:98–99.
14. Kubota S, Kitamura K, Matsui T, et al. Exercise-induced allergic reactions after achievement of desensitization to cow's milk and wheat. Pediatr Allergy Immunol. 2021; 32:1048–1055.
15. Horino S, Satou T, Masato N, et al. Provocation tests of food and exercise after immunotherapy. Arerugi. 2019; 68:1206–1212.
16. Wasserman RL, Factor J, Windom HH, et al. An approach to the office-based practice of food oral immunotherapy. J Allergy Clin Immunol Pract. 2021; 9:1826–1838.e8. □