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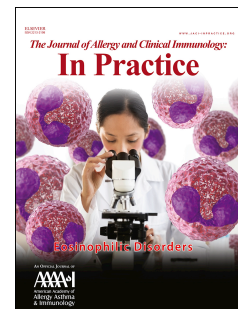
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Clinical communication

Long-term follow-up of fixed low-dose oral immunotherapy for children with wheat-induced anaphylaxis

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Motohiro Ebisawa has received lecture fees from DBV Technologies and Mylan EPD. Sakura Sato has received lecture fees from Mylan EPD. The other authors declare that they have no conflicts of interest.

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Clinical implications

For patients with wheat-induced anaphylaxis, continuing daily fixed low-dose OIT for several years increases the efficacy, safety, and immunological changes, and provides protective effects against anaphylactic reactions due to accidental wheat ingestion.

- 53 **Key words:** Anaphylaxis; Accidental exposure; Food allergy; Immunoglobulin E; Low-dose;
- 54 Oral food challenge; Oral immunotherapy; Wheat; ω -5 gliadin

Wheat allergy is one of the most common food allergies that induce anaphylaxis.¹ In Japan, wheat is the third leading cause of allergic symptoms due to accidental exposure.² Furthermore, patients with a history of wheat-induced anaphylaxis are less likely to acquire tolerance.³ Although oral immunotherapy (OIT) increases the threshold, adverse reactions commonly occur, with a risk of developing severe adverse reactions.¹ In previous wheat OIT trials, patients sometimes developed severe adverse reactions and discontinued the OIT protocol.⁴⁻⁶

In a previous work, we provided daily low-dose wheat OIT at a 1-year follow-up period.⁷ We found that desensitization to a low dose was induced more safely than conventional OIT.^{4,8} This study aimed to assess the long-term efficacy and safety of fixed low-dose wheat OIT.

The participants were patients aged ≥ 5 years who had a history of wheat-induced anaphylaxis and developed symptoms during an oral food challenge (OFC) with 53 mg of wheat protein. The details of the OFC and OIT protocols during the 1st year were presented in our previous report (Figure E1, available in the Online Repository).⁷ The historical control group was instructed to avoid wheat and received the 400–660 mg OFC yearly for up to 3 years. The attending physician assessed all allergic reactions after accidental wheat exposure. After 1 year, if the participants in the OIT group had been receiving 53 mg daily for at least 3 months, 400–660 mg OFC was administered after 2 weeks of wheat avoidance. Patients who reacted to the 400–660 mg OFC continued daily ingestion of 53 mg and received the 400–660 mg OFC annually for up to 3 years.

Those who passed the 400–660 mg OFC were defined as “short-term unresponsiveness to 400–660 mg” (Figure E1, available in the Online Repository). The historical control group was instructed to avoid wheat consumption and underwent OFC yearly to evaluate the threshold for up to 3 years.

The primary outcome was achieving short-term unresponsiveness after 3 years. The Cochran-Armitage trend test was used to examine the relationship between the duration of OIT and the frequency of adverse reactions. Twenty-nine patients received low-dose OIT, and 12 were classified into the historical control group (control group). All patients in both groups had a history of wheat-induced anaphylaxis. In the OIT group, the median wheat-, gluten-, and ω -5 gliadin-specific immunoglobulin E (IgE) levels were 278, 358, and 12.7 kU_A/L, respectively. The median age was significantly higher in the low-dose OIT group than in the control group ($P=.007$). The other characteristics were not significantly different between the groups (Table E1).

In the low-dose OIT group, no patients dropped out, and all (100%) achieved desensitization to 53 mg (median, 4 months) within 3 years. After 1, 2, and 3 years, the proportion of patients who achieved short-term unresponsiveness to 400–660 mg increased by 7% (two patients), 28% (eight patients), and 41% (12 patients), respectively. The number of patients who passed the 400–660 mg OFC was significantly higher in the OIT than in the control group (0%) ($P=.008$) (Figure 1).

The frequency of adverse reactions per OIT dosing significantly decreased annually (7.7%, 3.9%,

and 2.4% during the 1st, 2nd, and 3rd year, respectively) ($P < .001$). During the 2nd and 3rd years,

no anaphylaxis attributable to the OIT dose were reported (Table 1).

The proportion of patients who developed allergic reactions after accidental wheat exposure over

the 3-year period was 24% in the low-dose OIT group and 67% in the control group ($P = .01$). The

proportions of patients who developed anaphylaxis after accidental wheat exposure were 14%

and 50% in the low-dose OIT and control groups, respectively ($P = .04$) (Table 1).

Compared to the baseline, the median wheat-, gluten-, and ω -5 gliadin-specific IgE levels

significantly decreased to 89.3, 86.9, and 3.5 kU_A/L at 36 months ($P < .001$), respectively.

Furthermore, even in patients who could not achieve short-term unresponsiveness, the specific

IgE levels significantly decreased during the 3-year period ($P < .001$). In contrast, these changes

were not observed in the control group.

In the OIT group, the baseline gluten- and ω -5 gliadin-specific IgE levels in the short-term

unresponsiveness group were significantly lower than those in the treatment failure group ($P = .03$

and $P = .002$, respectively).

We report that the long-term fixed low-dose OIT was effective to create immunological changes,

which showed protective effects against accidental anaphylactic reactions for patients with wheat-

induced anaphylaxis.

Continuous ingestion of 53 mg for 3 years enabled 41% of patients to consume 400–660 mg,

109 which is much higher than the maintenance dose. The rate of short-term unresponsiveness

110 gradually increased annually to 41% at 3 years, similar to that of low-dose OIT for cow's milk.⁸

111 Regarding safety, the rate of adverse reactions significantly decreased annually, and no

112 anaphylactic symptoms developed after the 2nd year. Furthermore, no patients dropped out

113 because of adverse reactions, unlike the previously reported trials,^{4,5} and no patient developed

114 eosinophilic gastrointestinal disorders. Nowak et al. also reported decreased adverse reactions in

115 the 2nd year of OIT with a fixed target dose.⁴ These data suggested that continuing fixed low-

116 dose ingestion is a safe and feasible protocol.

117 Low-dose peanut OIT leads to a reduction in the number of allergic reactions due to accidental

118 peanut exposure.⁹ Similarly, in this trial, the rates of patients who developed allergic reactions

119 and anaphylaxis caused by accidental wheat exposure in the low-dose OIT group were

120 significantly lower than those in the control group.

121 This study had some limitations. First, this was not a randomized controlled trial. The median age

122 was significantly higher in the low-dose OIT group than in the control group. However, older

123 patients tend not to acquire tolerance in general.³ Second, OIT and OFC procedures were not

124 blinded. Third, we did not perform high-dose OFC for the assessment of OIT efficacy. Finally,

125 the participants in the OIT group received antihistamine administration until they achieved

126 desensitization to 53 mg.

In conclusion, for patients with wheat-induced anaphylaxis, continuing fixed low-dose OIT increases efficacy, safety, and immunological changes yearly, indicating a protective effect against wheat-induced anaphylaxis caused by accidental ingestion.

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Figure legends

Figure 1. Three-year outcomes of the low-dose OIT and historical control groups.

Dashed blue line shows the proportion that achieved desensitization to 53 mg in the low-dose OIT group. Solid red line and solid green line show the proportion that passed the 400–660 mg OFC in the low-dose OIT group and the historical control group, respectively.

OIT: oral immunotherapy, OFC: oral food challenge

Table 1. Adverse reactions at home in the OIT and control groups

Adverse reactions and treatments at home	Low-dose OIT group (n=29)			Historical control group (n=12)	<i>P</i> -value
	0–1 year	1–2 years	2–3 years	0–3 years	
Total number of intakes of OIT	9613	8513	6251		
Total number of adverse reactions	742 (7.7%)	331 (3.9%)	147 (2.4%)		
Mild	632 (6.6%)	306 (3.6%)	132 (2.1%)		
Moderate	110 (1.1%)	25 (0.3%)	15 (0.2%)		
Severe	0 (0.0%)	0 (0.0%)	0 (0.0%)		
Anaphylaxis	5 (0.05%)	0 (0.0%)	0 (0.0%)		
Total number of reactions requiring any	162 (1.7%)	61 (0.7%)	52 (0.8%)		

treatments				
Antihistamine	158 (1.6%)	49 (0.6%)	43 (0.7%)	
Steroid	26 (0.3%)	19 (0.2%)	19 (0.3%)	
β_2 agonist inhalation	85 (0.9%)	42 (0.5%)	26 (0.4%)	
Adrenaline	3 (0.03%)	0 (0.0%)	0 (0.0%)	
The number of patients who developed allergic reactions after accidental exposure				
The number of patients who developed anaphylaxis after accidental exposure		n=7 (24%)	n=8 (67%)	.01
The number of patients who developed anaphylaxis after accidental exposure				
		n=4 (14%)	n=6 (50%)	.04

The severity of symptoms was classified as mild, moderate, or severe, based on the Japanese guidelines for food allergy. None of the patients developed EGID in both groups.

Severe reactions after accidental exposure were observed in one patient each in both groups.

OIT: oral immunotherapy, EGID: eosinophilic gastrointestinal disorders

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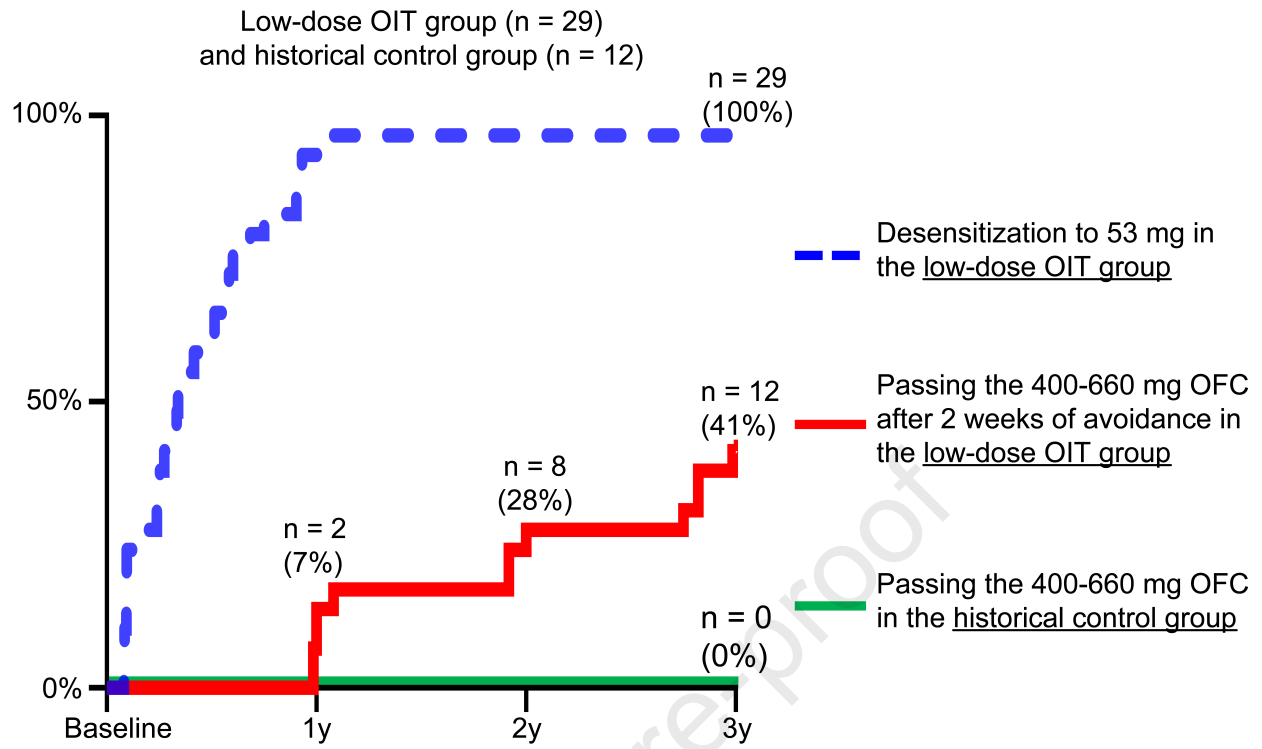


Figure E1. Flowchart of participant selection (A) and low-dose OIT protocol (B).

Patients who passed the 400–660 mg OFC after 2 weeks of wheat avoidance were defined as having short-term unresponsiveness to 400–660 mg and could consume processed food containing up to 400–660 mg at home twice a week. The primary outcome was achieving short-term unresponsiveness after 3 years.

OIT: oral immunotherapy, OFC: oral food challenge

Table E1. Baseline characteristics of patients in the low-dose OIT and historical control groups

		Low-dose OIT group (n=29)	Historical control group (n=12)	P value
Age (years)		6.7 (6.3–7.9)	5.9 (5.0–6.9)	0.007
Male, n (%)		18 (62%)	9 (75%)	0.43
History of anaphylaxis to wheat, n (%)		27 (100%)	12 (100%)	–
Number of incidences of anaphylaxes		2 (1–3)	1 (1–2)	0.26
History of severe anaphylaxis to wheat, n (%)		4 (14%)	3 (25%)	0.40
Current, Complications, n (%)	BA	12 (41%)	7 (58%)	0.32
	AD	10 (34%)	3 (25%)	0.55
	AR	9 (31%)	6 (50%)	0.25
Severity of symptoms during baseline OFC		Mild: 3, Moderate: 22, Severe: 4	Mild: 1, Moderate: 11, Severe: 0	>0.99
Threshold of baseline OFC (mg)		53 (13.3–53)	13.3 (16.6–53)	0.82
Total IgE (IU/L)		923 (543–2710)	493 (307–1325)	0.14
Specific IgE (kU _A /L)	Wheat	278 (89.1–501)	72.4 (22.5–316.8)	0.16

Gluten	358 (141–643)	68.5 (33–636)	0.39
ω -5 gliadin	12.7 (4.2–32.9)	15.6 (4.0–40.5)	0.73

Patients enrolled in 2014 July to 2015 March are identical to those in previous article.

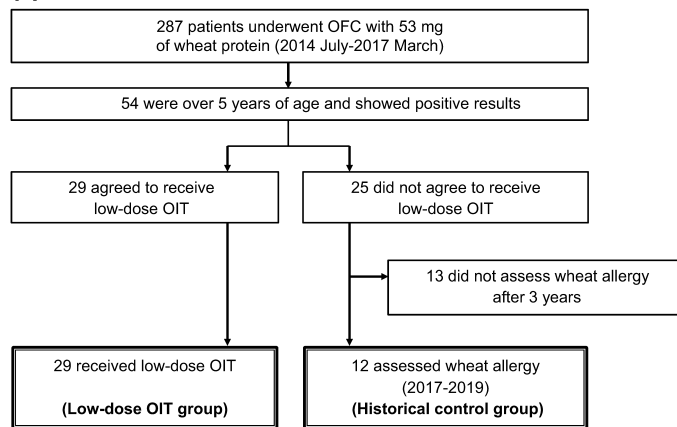
The threshold dose was defined as the accumulated dose that was ingested by patients when the objective symptoms developed, or subjective symptoms lasted for at least 30 minutes.

Gluten-specific IgE was not measured for three patients in the historical control group.

OIT: oral immunotherapy, BA: bronchial asthma, AD: atopic dermatitis, AR: allergic rhinitis, OFC:

oral food challenge

A



B

