

# Immunotherapy for Food Allergy

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## ABSTRACT

Although the current standard care for patients with food allergy is based on avoidance of the trigger foods with hope of possible gain of tolerance, increasing number of studies have shown that oral immunotherapy is a promising approach. Understanding the transcutaneous sensitization and oral immune tolerance to food antigens has shifted focus of treatment and prevention. However, more studies are warranted to elucidate the underlying mechanisms and to clarify the indication criteria to which type of patients this therapy should be applied. Easy and uncontrolled use of elimination diets for atopic dermatitis might have increased and exacerbated food allergy, and thorough innovation of our whole concept for food allergy is now required.

## KEY WORDS

food allergy, immunotherapy, tolerance induction

## INTRODUCTION

My task is a review on the immunotherapy for food allergy in a special issue on the immunotherapy for allergic diseases. The immunotherapy for food allergy may be somewhat different from the immunotherapy for other allergic diseases, because it is not recognized widely and the practical methods are not established yet, although as a matter of fact there is a fairly long history for oral immunotherapy for food allergy. The number of successful reports of immunotherapy (tolerance induction) for food allergy has been increasing in recent years, and the enormous hope for positive and radical treatment of food allergy is coming in sight. Furthermore, the understanding of oral immune tolerance and the results of some epidemiological studies are seriously demanding us thorough reconsideration about the pathogenesis of food allergy and our current policy to prevent or manage food allergy.

## IMMUNOTHERAPY (TOLERANCE INDUCTION) FOR FOOD ALLERGY

### INJECTION IMMUNOTHERAPY

Although there are rare successful reports of injection immunotherapy on fish allergy<sup>1</sup> and on peanut allergy,<sup>2</sup> studies in 1990s indicated that subcutaneous injection immunotherapy for peanut allergy was not recommended because of unacceptably high rate of adverse systemic reactions.<sup>3</sup> On the contrary, increas-

ing number of reports on oral immunotherapy for food allergy has been being published recently.

## TERMINOLOGY OF ORAL IMMUNOTHERAPY FOR FOOD ALLERGY

Terminology for the oral immunotherapy for food allergy based on an escalating dosage of orally ingested foods or food protein has not been unified. Copying after the examples of other immunotherapy, such as subcutaneous immunotherapy (SCIT) or sublingual immunotherapy (SLIT), the term of oral immunotherapy should be appropriate. Though some authors have expressed their methods as oral desensitization or oral hyposensitization, these terms should be closely associated with the functioning mechanisms, then these are suitable if the effect of these treatments to improve sensitization, in other words to reduce or delete specific IgE to the foods used for the treatment, becomes secure. The purpose of these treatments is to enable patients of food allergy to ingest offending foods to some extent without obvious adverse reactions, and I myself call our own method specific oral tolerance induction (SOTI).

## THE ORIGINATOR

Oral immunotherapy for food allergy started to get a wide range of attention only for the past few years. The number of publication identified by searching PubMed with the key words of "food allergy & immunotherapy" or "food allergy & oral tolerance" started

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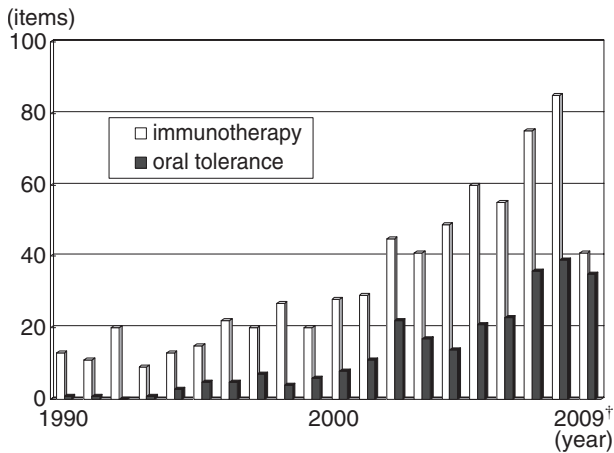
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**Fig. 1** The numbers of published papers on immunotherapy or oral tolerance for food allergy. The numbers of published papers found by searching PubMed with keywords of “food allergy & immunotherapy” or “food allergy & oral tolerance” since 1990 are shown. †Searched on September 1, 2009.

to increase after 2002 as indicated in Figure 1. However, Brown<sup>4</sup> introduced a paper written by Schofield<sup>5</sup> published in 1908 as a very old successful case of oral immunotherapy for egg allergy.

The title of Schofield’s paper is “A case of egg poisoning”, not “A case of egg allergy”, but we have to remember that it was 1906 that von Pirquet coined the term “allergy” de novo. And you will realize easily that the case of a 13-year old boy described there was no doubt a sample of typical severe egg allergy. Schofield gave the boy a pill daily, which contained gradually increasing amounts of raw egg starting from 1/10,000th of an egg, and the boy eventually could eat a whole egg 8 months after.

## THE PROGRESS

Thereafter, the experiences of the oral immunotherapy for food allergy had been reported sporadically from European countries such as Spain, Italy, German, *et al.*, but they seemed to be treated as rather heresy, and did not arrest much attention. The quality of reports or studies varied greatly, and some were just case reports of small number, and each report utilized individual protocols based on their own experiences. It is very interesting to note that *Monographs in Allergy* featured a pro/con debate on oral desensitization for cow’s milk allergy in 1996,<sup>6,7</sup> when the journal had been discontinued. In 1990s, a few clinical reports on oral immunotherapy for food allergy appeared every year, sporadically or repeatedly by some groups, and the quality of the study became better, and got broader attention gradually. Enrique *et al.*<sup>8</sup> reported the effectiveness of sublingual immunotherapy for hazelnut allergy in a double-blind fashion, and Longo *et al.*<sup>9</sup> reported the one-year follow up of oral tolerance induction for severe milk allergy, in

**Table 1** Classification of oral immunotherapy (tolerance induction) for food allergy

Tempo	Rush(days-weeks)
	Slow(months-years)
	Rush → Slow
Route	Oral (ingestion)
	Sublingual
	Sublingual + oral
Setting	In hospital
	At home (and outpatient clinic)
	In hospital → At home

which they showed high-rate acquisition of tolerance in active group and virtually no improvement in avoidance group. Then, Skripak *et al.*<sup>10</sup> clearly proved that deliberate oral intake of cow’s milk protein for several months was safe and efficacious in tolerizing children with cow’s milk allergy in a double-blind, placebo-controlled fashion. And Martorell *et al.*<sup>11</sup> and Staden *et al.*<sup>12</sup> reported the successful results of rush oral immunotherapy carried out during only 3-7 days.

The protocols of the oral immunotherapy reported so far are classified as Table 1.

## EVALUATION OF THE ORAL IMMUNOTHERAPY FOR FOOD ALLERGY

At the present day, though there are various opinions about the oral immunotherapy for food allergy, affirmative ones are increasing. Niggemann *et al.*<sup>13</sup> summarized in a review article in 2006 that the body of scientific evidence concerning specific oral tolerance induction was still rather poor, and before SOTI could be recommended for the daily praxis, more studies were warranted to clarify whether certain patients might profit from SOTI and to understand the underlying mechanism. Then, however, they published new data of SOTI under the protocols performed at home on a daily basis during a median of 21 months in 2007,<sup>14</sup> and also under the rush protocols performed in hospital, reaching the goal during 3 to 7 days in 2008.<sup>12</sup> Beyer & Wahn<sup>15</sup> in 2008 conceded that several studies had shown that oral immunotherapy was a promising approach, especially in patients with severe and persistent food allergy, and that side effects were frequent but seemed controllable. But they concluded that treatment protocols had been performed in highly supervised research settings, and until more experience was gained from larger long-term studies, oral immunotherapy should not be tried in clinical practice settings. Shaker & Woodmansee<sup>16</sup> introduced a new concept about the timing of weaning and the introduction of solid foods, explaining that avoidance of highly allergenic foods beyond 4-6 months might not be effective at preventing the development of food allergy in most children, and the effect of specific early introduction of aller-

**Table 2** Rush SOTI for egg allergy: Background of subjects and the results. Six new cases are added to the original data cited as reference 20.

Subject number	Sex	Age	Age of last anaphylaxis by cooked egg	Complications	Threshold		Days of rush SOTI <sup>†</sup>	Symptoms during treatment
					before (g)	after (g)		
001	F	9y8m	9y2m	BA, AD	0.360	>60	18 (13)	WH, UR, AP
002	M	8y5m	8y0m	BA, AD, AR	0.012	>60	13 (9)	UR
003	M	12y0m	11y3m	BA, AD, AR	0.296	>60	9 (7)	AP
004	F	7y2m	6y9m	BA, AD, AC	0.200	>60	10 (8)	WH, UR
005	M	9y4m	8y10m	BA, AD	0.088	>60	15 (11)	AP, DI
006	M	11y4m	10y10m	BA, AD	0.104	>60	11 (9)	AP, DI
007	M	11y3m	10y10m	AD, AR, AC	0.144	>60	15 (10)	WH, UR, AP
008	F	11y2m	11y0m	AD	0.752	>60	10 (8)	UR, AP
009	M	6y9m	6y4m	BA, AD, AR	0.752	>60	14 (9)	WH, UR, DI
010	M	7y8m	7y6m	BA	0.011	>60	15 (11)	WH, UR
011	F	7y9m	3y0m	BA, AD	0.030	>60	15 (11)	WH, UR
012	M	6y9m	3y2m	BA	0.013	>60	15 (11)	WH, UR, AP, DI
Median		8y7m			0.124 (raw EW)	>60 (cooked egg)	14.5 (9.5)	

SOTI, specific oral tolerance induction; EW, egg white; BA, bronchial asthma; AD, atopic dermatitis; AR, allergic rhinitis; AC, allergic conjunctivitis; WH, wheezing; UR, urticaria; AP, abdominal pain; DI, diarrhea.

<sup>†</sup>Figures in parenthesis do not include the days staying at home without increase in the dose of egg.

genic foods was being investigated. At the same time, they expressed their negative attitude about oral immunotherapy, saying that oral immunotherapy was under investigation but might be limited in future use by several factors, including a significant rate of allergic reactions.

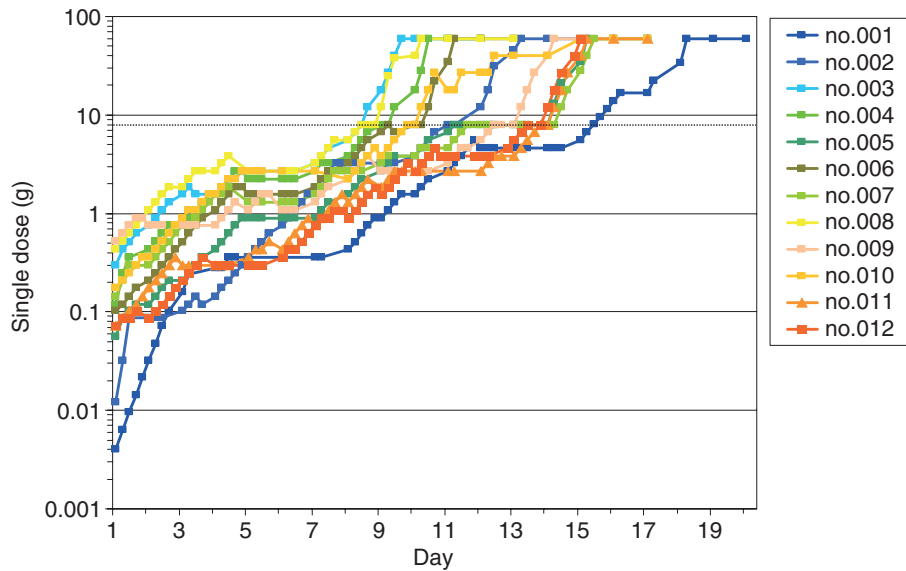
There are more affirmative and positive opinions. Burks *et al.*<sup>17</sup> asserted that increased understanding of the mechanisms involved in tolerance had shifted focus of treatment and prevention toward inducing tolerance, although the current standard of care for patients with food allergies was based on avoidance of the trigger, and continued that data from early-phase clinical trials suggested both sublingual and oral immunotherapy were effective in reducing sensitivity to allergens. And Barbi *et al.*<sup>18</sup> said that “We hypothesize that widespread and uncontrolled use of elimination diets for atopic dermatitis may have played a role in the increase of allergy and anaphylaxis. Specific oral tolerance induction may be a possible therapeutic strategy.” Patriarca has been one of the pioneers of this field, and he and his colleagues reported clinical data repeatedly, and wound up their recent review article<sup>19</sup> by writing that “The only etiologic treatment of food allergy is specific desensitization. Sublingual-oral-specific desensitization has been used by our group for the treatment of food-allergic patients with a high percentage of success.”

### OUR EXPERIENCES

We consider the injection immunotherapy for pollen allergy or nasal allergy is a very important and rare radical treatment, and we are carrying it out in a rush fashion in which patients receive allergen shots sev-

eral times a day in hospital.<sup>20</sup> And by getting the knowledge concerning the oral immune tolerance, we began to think of rush immunotherapy for food allergy through oral route instead of injection. After the certification by the institutional ethical committee, we started the first trial of rush specific oral tolerance induction (rush SOTI) in September, 2007. The report about our first 6 cases with severe egg allergy treated by rush SOTI and the follow up to 1 year has been accepted by *Allergology International*, and is coming out soon.<sup>21</sup>

Adding 6 cases to the report of first 6 cases included in the previous report,<sup>21</sup> the summary of 12 cases with anaphylaxis-type severe egg allergy treated by rush SOTI is shown in Table 2 and in Figure 2. All subjects, whose threshold to raw egg white was 0.124 g in median (0.011-0.752 g), acquired oral tolerance to more than one whole cooked-egg (60 g), and it took only 14.5 days (9-18 days). In this procedure, material of egg was changed from raw egg-white powder to cooked egg when the dose reached 8 g because of the taste and the convenience in daily life. None experienced any serious reaction requiring adrenaline injection. Among 640 dosing of egg materials during rush SOTI for these 12 subjects, we experienced 118 very mild reactions (itch of mouth or throat, mild skin rash), 36 mild reactions (wide range of skin rash, transient complaints of digestive or respiratory system), and 2 moderate reactions (skin rash across the whole body, prolonged or repeated digestive system, or mild dyspnea), but no case of severe reactions including shock. The medication used to relieve these adverse reactions were 33 oral antihistamines, 15 inhalations of salbutamol, 1 oral prednis-



**Fig. 2** The individual process of rush SOTI for egg allergy to reach a whole egg. The abscissa expresses the days after starting rush SOTI. The ordinate expresses the single doses of egg plotted in logarithmic scale. Rush SOTI was started with powdered raw egg white, and when the dose reached 8 g, it was changed to cooked egg. Six new cases are added to the original figure which has been shown in the reference 21.

lolone, and 2 injections of antihistamine. From the analysis of the first 6 cases, specific IgE to egg white or ovomucoid tended to increase at the end of rush SOTI, thereafter tended to decrease, and decreased significantly after 12 months. Egg white-specific IgG<sub>4</sub> levels increased significantly only after 12 months. At the moment, the immunological mechanisms occurring during rush SOTI are not clear. Although further studies involving a large group of patients and thorough analyses of the mechanisms are needed, we consider that rush SOTI is a promising maneuver that would replace allergen avoidance as the therapy for food allergy.

We do not consider that the rush method is superior to the procedure carried out slowly at home, spending several months to reach the goal, that is slow SOTI. Actually, we are treating much more patients with slow SOTI than with rush SOTI. We assume the food challenge test as a step to evaluate the threshold to tell them the dose to start ingestion of the food safely, not to just decree the absolute elimination to them when the result is positive.

### ORAL IMMUNE TOLERANCE

One of the theoretical bases of oral immunotherapy is oral immune tolerance, which is not a new idea at all, and has been a subject of research in immunology for nearly 100 years. Already in 1911, Wells & Osborne<sup>22</sup> clearly showed that guinea pigs fed on corn did not come up with anaphylactic responses when sensitized and challenged by a corn protein. Vaz *et al.*<sup>23</sup> showed that one dose of 20 mg OVA administered

orally 7 or 14 days before parenteral immunization inhibited the response of IgE and IgG almost completely. Ngan & Kind<sup>24</sup> found that the inhibitory effect of OVA administered orally was maintained at the dose of only 100 µg/mouse. Peng *et al.*<sup>25</sup> investigated the immunological consequences of feeding a protein antigen to previously immunized animals, and found that oral tolerance depended on the immune status of the animal and was controlled by antigen dose, time and frequency of feeding.

Now, some mechanisms of oral immune tolerance have been elucidated from investigation of animal model. High-dose tolerance is mediated by lymphocyte anergy or clonal deletion, and low-dose tolerance is mediated by some kinds of regulatory T cells and some cytokines, such as IL-10 and TGF-β.<sup>26</sup> More mechanistic studies are mandatory to test whether these phenomena are similar in human subjects and to resolve the process predisposing some individuals to food allergy.

### PREVENTION OF FOOD ALLERGY

Elimination of highly allergic foods is plausible to prevent the development of food allergy, and many trials of preventive elimination for high-risk babies were actually performed, most of them turning out failure or limited success. Concerning the timing of solid food introduction, the delay does not seem to prevent the development of food allergy, but may enhance sensitization to some foods.<sup>27,28</sup> Anderson *et al.*<sup>29</sup> stated that currently-available research suggested that introducing solids at 4-6 months might result in the lowest al-

lergy risk, and that the recommended duration of exclusive breastfeeding and age of introduction of solids were confirmed to be 6 months, but no later. American Academy of Pediatrics (AAP) had recommended in 2000 for high-risk infants not to introduce solid foods until 6 months of age, with dairy products delayed until 1 year, egg until 2 years, and peanuts, nuts, and fish until 3 years of age, without showing secure evidences.<sup>30</sup> AAP made a revised statement in 2008 to replace the former recommendation,<sup>31</sup> and they recommended exclusive breastfeeding for at least 4 months for infants at high risk of developing atopic disease, but said that there is no current convincing evidence that delaying solid food introduction beyond 4-6 months of age has a significant protective effect on the development of atopic disease, including fish, eggs, and foods containing peanut protein. Following this, an interesting report by Du Toit *et al.*<sup>32</sup> came out. They demonstrated that Jewish children in the UK had a prevalence of peanut allergy that was 10-fold higher than that in Israel (1.85% vs 0.17%,  $P < 0.001$ ), and Israeli infants consumed peanut in high quantities in the first year of life, whereas UK infants avoided peanuts. They raised an important proposition that whether early introduction of peanut during infancy, rather than avoidance, would prevent the development of peanut allergy. Their data might be a good example of oral immune tolerance in human model.

I want to refer to new topics on atopic dermatitis. Even though the close relation between the sensitization to foods and atopic eczema is obvious, this does not necessarily mean the causative importance of food allergy for atopic eczema. The pathogenesis of atopic dermatitis is not fully clarified, but new theory was brought to our knowledge recently. Elias *et al.*<sup>33</sup> assessed evidences that inflammation in atopic dermatitis results from inherited and acquired insults to the barrier abnormality of skin, including loss-of-function mutation in the gene encoding filaggrin. And further, Lack<sup>34</sup> proposed "Dual-allergen-exposure hypothesis for pathogenesis for food allergy", suggesting that sensitization to food allergen occurs through environmental exposure through the skin and that oral consumption of food allergen induces oral tolerance.

## CONCLUSION

Probably, we are standing at a very important turning point concerning the management of food allergy. Understanding of the transcutaneous sensitization and oral immunotolerance to food antigens are precipitating thorough innovation of our whole concept for the pathogenesis of food allergy. Oral immunotherapy or tolerance induction for food allergy by deliberate oral intake of foods which cause allergic reactions seems a promising approach which liberates patients from persistent anxious of sudden and serious

symptoms and endless effort to avoid a trace of certain foods in daily life. This concept is quite different from the most basic principle of the management of allergic diseases which says "To reduce or avoid the exposure to relevant allergens." The body of scientific evidences for the therapy is still poor, and the therapy naturally possesses the risk of inducing allergic reactions. More studies are warranted to elucidate the underlying mechanisms and to establish safer and securer practical methods urgently.

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