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Epicutaneous Immunotherapy for Food Allergy: A Randomized, Double-Blind, Placebo-Controlled Cross-Over Study

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Abstract

Objective: Oral Immunotherapy (OIT) is widely practiced as a treatment option for food allergies. However, the evidence to support its clinical efficacy is insufficient, and the process is associated with serious side effects such as anaphylaxis; thus, it is not recommended as a general treatment modality. Epicutaneous Immunotherapy (EPIT) has lower risks of adverse effects upon comparison with OIT; nonetheless, clinical experience in the application of EPIT for treating food allergy is limited. Therefore, we performed a randomized, double-blind, placebo-controlled, cross-over study to evaluate the efficacy of EPIT in the treatment of pediatric food allergy.

Methods: The study population included 13 children with food allergies (egg: n=8; milk: n=5; age: 5-18 years). An allergen or a placebo was applied to the skin for 48 h, 3 times a week, for 8 weeks. The effects were evaluated according to the cumulative tolerated dose in an oral food challenge. At the end of the first and second periods, each subject underwent an oral food challenge in a hospital thrice before the study.

Results: In egg allergy, the cumulative tolerance dose increased significantly in the allergen-EPIT stage. An escalation in milk allergy was also noticed, but it was insignificant. Significant increase was not observed in either of the placebo-EPIT stages. In addition, no cases demonstrated serious systemic adverse events.

Conclusion: EPIT can be useful for the treatment of pediatric food allergies.

Keywords: Oral immunotherapy; Epicutaneous immunotherapy; Double-blind placebo-controlled cross-over study; Egg allergy; Milk allergy; Oral food challenge; Allergen sensitization

Abbreviations: OIT: Oral Immunotherapy; EPIT: Epicutaneous Immunotherapy; SCIT: Subcutaneous Injection Immunotherapy; SLIT: Sublingual Immunotherapy; TARC: Thymus and Activation-Regulated Chemokine

Introduction

The treatment of food allergy is based on precisely identifying and removing the causal agent and treating the induced symptoms. Immunotherapy, which is the fundamental treatment modality for various allergic diseases, including food allergy, is being actively practiced in recent days. In 1966, Baba [1] reported that oral immunotherapy (OIT), with a modification of the method reported by Dees [2] was useful in the treatment of cow's milk allergy. Thereafter, OIT was also testified to be useful in the treatment of other allergies, including egg and peanut allergy [3-6]. Furthermore, Itoh et al. [7] documented the effectiveness of rush specific oral tolerance induction in children with severe egg allergy, and the use of OIT in the treatment of food allergy was re-examined and implemented across several facilities. Although OIT has a therapeutic effect, it is associated with a high risk of anaphylaxis; thus, it has not been accepted as a standard method of food allergy treatment [8].

In this context, epicutaneous immunotherapy (EPIT), which exploits the skin immune system, has been studied since the 1950s. Blamoutier et al. [9] and Eichenberger et al. [10] investigated the usefulness of EPIT in managing hay fever, and it was expected to be a safe and convenient treatment. Later, in 2009, EPIT was proven to display the same effect as subcutaneous injection immunotherapy (SCIT) in mouse models of allergy that included house dust and peanut [11]. Furthermore, Senti et al. [12] researched the usefulness of EPIT in the treatment of hay fever using a double-blind, placebo-controlled study and stated no serious systemic side reactions. In addition, Dupont et al. [13] administered EPIT for 90 days in patients with milk allergy by employing a double-blind, placebo-controlled, cross-over study. The researcher reported an increase in the cumulative tolerated dose in an oral food challenge and confirmed that no patients experienced serious side effects.

Since then, reports on the usefulness of EPIT in the treatment of allergies, including peanut allergy, have continued to appear [14,15]. However, clinical experience in the application of EPIT for treating food allergy is limited. Therefore, in this study, we performed a

randomized, double-blind, placebo-controlled, cross-over study to evaluate the efficacy of EPIT in the treatment of pediatric food allergy.

Materials and Methods

Patients

The patients included 13 children with food allergies who visited the Pediatric Department of Fraternity Memorial Hospital (egg: n=8; milk: n=5). The condition was diagnosed based on the results of an oral food challenge. The underlying diseases included atopic dermatitis and bronchial asthma. Table 1 presents the background characteristics of the patients.

Case No.	Gender	Age (years)	Disease	Food Allergy	Anaphylaxis	EPIT allergen
1	M	6	BA, AD	Egg, Milk	Egg	Egg
2	F	9	BA, AD	Egg, Milk	Egg, Milk	Egg
3	M	14	AD, BA	Egg, Milk	Egg	Egg
4	M	7	AD, BA	Egg	Egg	Egg
5	M	3	AD	Egg	Egg	Egg
6	M	7	AD, BA	Egg	Egg	Egg
7	M	6	BA	Egg, Milk	Egg	Egg
8	M	6	AD	Egg, Fish Egg, Peanuts	Egg	Egg
9	F	5	ADs	Milk, Soba	Milk	Milk
10	M	18	AD, BA	Milk	Milk	Milk
11	F	6	AD	Milk, Egg, Wheat	Milk	Milk
12	M	12	AD, BA	Milk	Milk	Milk
13	M	7	AD, BA	Milk	Milk	Milk

Table 1: Patient characteristics. M: Male; F: Female; AD: Atopic Dermatitis; BA: Bronchial Asthma.

Study protocol

A randomized, double-blind, placebo-controlled, cross-over study was performed to investigate the effectiveness and safety of EPIT. The antigens used for EPIT were hen's egg protein for children with egg allergy and milk protein for children with milk allergy. Distilled water was utilized in the control treatment.

Epicutaneous Immunotherapy (EPIT)

A Finn Chambers® (SmartPractice®) skin allergy patch test was used for EPIT. The allergen was applied to intact skin on the outside of the upper arm. Dried egg white and skimmed cow's milk were employed as the allergens. Based on the literature [13], the allergen dosage was 1 mg-/-time for dried egg white as well as skimmed cow's milk. A quantitative continuation method was performed thrice a week, every 48 h, to evaluate the effects. Distilled water, applied for allergen dissolution, was used as a control.

The randomized, double-blind, placebo-controlled, cross-over study

In period 1, the subjects were selected to receive either the allergens or the control reagents in a blinded manner. In period 2, the patients who received the allergen in period 1 were switched to the control and vice-versa. Each period lasted for 8 weeks (Figure 1).

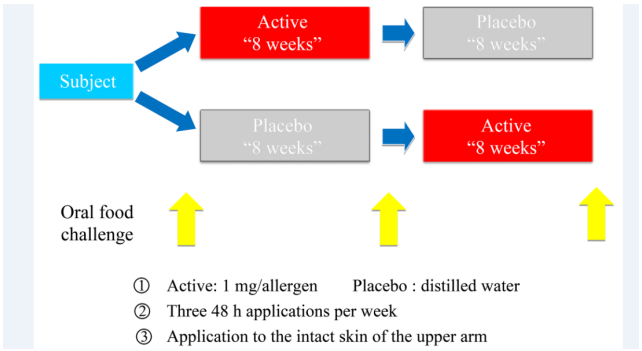

Figure 1: The double-blind, placebo-controlled, cross-over study of EPIT.

The oral food challenge

The first oral food challenge was conducted using the open method within the first 2 months. A second challenge was performed within 1 week after the end of period 1, and a third one was performed within 1 week of the end of period 2. During all challenges, the cumulative tolerated dose of the allergen that induced immediate allergic symptoms was measured as the oral food challenge threshold.

Measurement of serum markers

The serum antigen-specific IgE antibodies were measured using the Fluoro Enzyme Immunoassay (ImmunoCAP System, Phadia, Uppsala, Sweden,) and Thymus Activation-Regulated Chemokine (TARC) values were evaluated by ELISA, before and after the study, respectively.

Side effects

During the study period, the subjects carried an "adrenaline auto-injection" device (Epipen®), and when side reactions, including allergic symptoms, were induced, the antihistamines and corticosteroids were administered (topically or orally) depending on the degree of symptoms.

Complete removal of the allergen

Oral intake of the allergen was prohibited during the study period, and the state of complete elimination was continued throughout the study.

Statistical analysis

The statistical analyses were conducted with the help of SPSS software program (IBM SPSS Statistics, Version 22 for Windows, IBM, Chicago, IL). The data were analyzed using a non-parametric Mann-Whitney U-test. $p<0.05$ was considered to indicate statistical significance.

Ethical considerations

The present study was performed in accordance with the Declaration of Helsinki and was approved by the Hospital Ethics Committee (approval number 93). The children and their guardians provided written consent after receiving a written explanation.

Results

Changes in the cumulative tolerated dose in 8 children with egg allergy

In the allergen phase, the value measured after treatment (g, median [range]: 3.2 [1.20-17.50]) was significantly increased upon comparison with the previous value (0.55 [0.31-1.75]) (p=0.018) (Figure 2a). On the other hand, in the placebo phase, the value measured after treatment with the control agent (0.75 [0.31-8.00]) did not differ from the previous one (0.75 [0.50-8.00]) to a statistically significant extent (p=0.789) (Figure 2b).

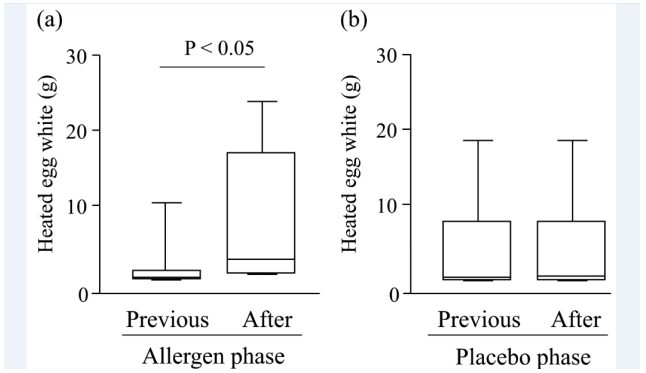

Figure 2: Changes in the cumulative tolerated dose in 8 children with egg allergy (a) In the allergen phase, the value measured after treatment (g, median [range], 3.2 [1.20-17.50]) was significantly increased in comparison to the previous value (0.55 [0.31-1.75]) (p=0.0179), (b) There was no significant difference between the values measured before and after the placebo phase (g, median [range], 0.75 [0.31-8.00] *vs.* 0.75 [0.50-8.00], respectively) (p=0.789).

Changes in the cumulative tolerated dose in 5 children with milk allergy

Although the posterior value (mL, median [range]: 75.0 [23.50-125.0]) tended to increase when compared with the previous value (24.0 [3.25-50.0]), there was no statistically significant difference (p=0.116) (Figure 3a). In the placebo phase, the value obtained after treatment with the control reagent (25.0 [13.5-53.5]) did not differ from the previous one (15.0 [3.8-33.5]) to a statistically significant extent (p=0.600) (Figure 3b).

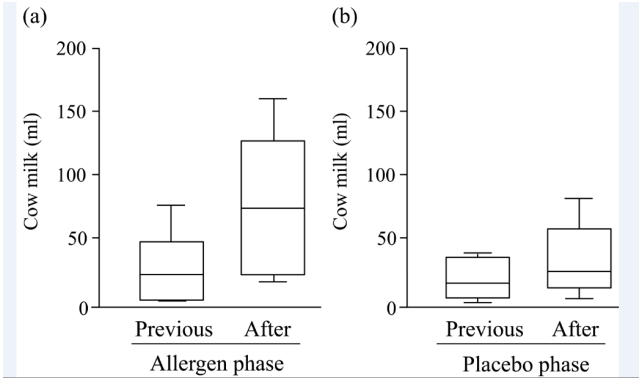

Figure 3: Changes in the cumulative tolerated dose of 5 children with milk allergy (a) Although the posterior value (mL, median [range], 75.0 [23.50-125.0]) tended to increase as compared with the previous value (24.0 [3.25-50.0]), there was no statistically significant difference (p=0.116), (b) There was no significant difference between the values measured before and after the placebo phase (mL, median [range], 15.0 [3.8-33.5] *vs.* 25.0 [13.5-53.5], respectively) (p=0.600).

Trend in the cumulative tolerated dose in patients who received the allergen before the placebo

In this study, 3 of the 13 patients received the allergen before the placebo. The cumulative tolerated dose of two patients who displayed an increase in cumulative tolerated dose in the allergen phase was stably maintained, even after the subsequent 8-week placebo phase (Figure 4).

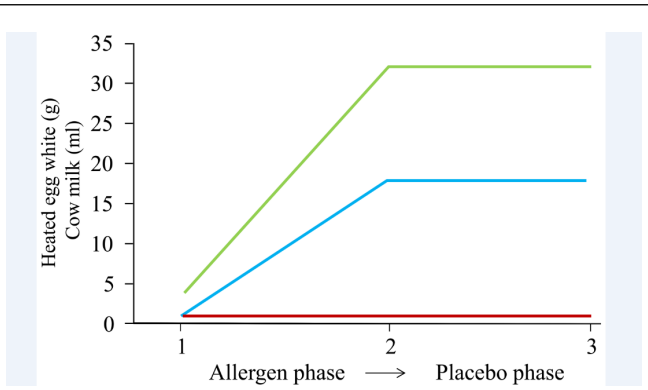

Figure 4: Trends in the cumulative tolerated dose in cases in which the allergen phase preceded the placebo phase. The cumulative tolerated doses of 2 patients who values showed in the allergen phase were maintained, even after the 8-week placebo phase. The top panel of the figure shows the results of the milk allergy case; the middle and lower panels show the results of the egg allergy cases.

Changes in the serum allergen-specific IgE antibody values

The serum egg white-specific IgE antibody levels were measured in 7 of the 8 patients, while milk-specific IgE antibody levels were measured in 4 of the 5 patients using the corresponding allergens. The levels measured before and after the study did not differ to a statistically significant extent (Figures 5a and 5b).

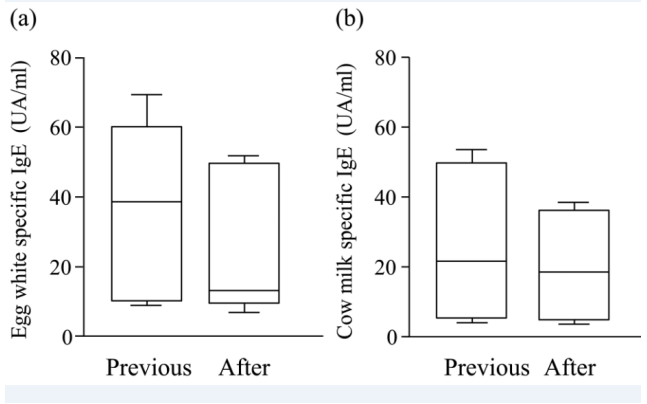

Figure 5: Changes in the serum egg white- and milk-specific IgE antibody values (a, b) There were no obvious fluctuations in the serum egg white- and milk-specific IgE antibody value.

Changes in the serum TARC values

The serum TARC values were measured in 7 of the 13 patients. The values measured before and after the study did not differ to a statistically significant extent (Figure 5C).

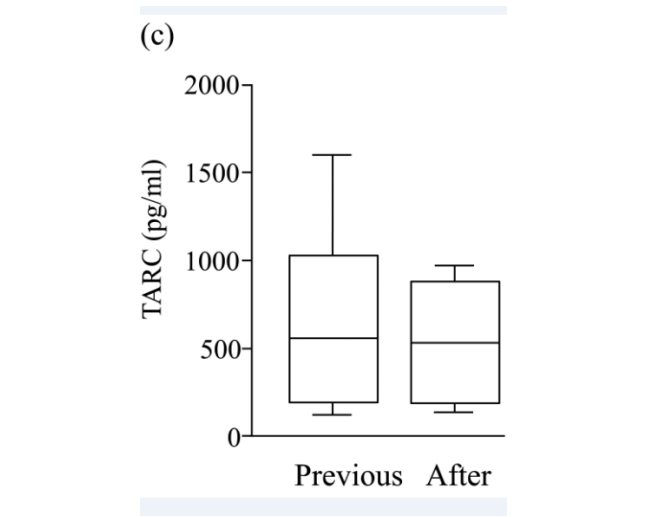

Figure 5: Changes in the serum TARC values (c) There were no obvious changes in the serum TARC values.

Adverse events

Table 2 lists the adverse events that occurred during the course of the study. All such events were localized skin reactions, and none of the patients experienced systemic allergic reactions, such as anaphylaxis. Topical skin reactions included itching and redness at the application site; however, these symptoms eventually disappeared and the study was continued in all cases.

	Active phase	Placebo phase
	(n=13)	(n=13)
Local events	6	4
Systemic events	0	0

Table 2: Adverse events during the course of the study. Local events: itching/eruption (transient and not worsening). All adverse events that appeared were localized skin reactions. No patients developed systemic allergic reactions such as anaphylaxis.

Progress of the primary disease

None of the patients experienced worsening of their original disease during the course of this study.

Discussion and Conclusion

The skin is considered to be a site at which the allergic symptoms manifest, and increased attention is recently being paid to the skin as a site of allergen sensitization. Regarding preventing such a sensitization, the barrier function of the skin and its role in moisture retention are important in preventing allergic diseases [16]. Even in food allergies, percutaneous sensitization is a serious concern, and it has been pointed out that its prevention can deter the onset and worsening of the disease [17].

Matsumoto et al. [18] approached the essence of percutaneous sensitization from a novel perspective called per "-eczema" tous. If we consider the barrier function of the skin to be equivalent to blocking the invasion of the antigen, EPIT is a so-called challenge to the barrier function of the skin and, therefore, may be viewed as a reckless treatment. However, we selected EPIT as a safer form of immunotherapy and examined its usefulness. Although the population size of the present double-blind placebo-controlled cross-over study was small, it adequately demonstrated the effectiveness of EPIT in treating egg allergy. Although it was not significant in milk allergy, the cumulative tolerated dose exhibited an upward trend. Moreover, no serious adverse events were observed.

Furthermore, in 2 cases, a significant increase in the cumulative tolerated dose was observed during the allergen phase, which was retained even after the 8-week placebo phaseAll these results were obtained during the study period, when the allergen was completely removed, that is, without OIT. Furthermore, the skin was not consistently healthy. Although the patch was applied to a healthy skin [19], the tape was pasted and removed 3 times per week (>48 times in 16 weeks) during EPIT, and a large number of the patients (12/13, 92.3%) suffered from atopic dermatitis as an underlying diseaseAt the very least, it can be said that the recent "complete removal" of the allergen and "the condition of the patients' skin" [17] would not have improved the patients' food allergies.

The immunological mechanisms involved in EPIT have not yet been elucidated; however, similar to OIT and SCIT, the presence of regulatory T cells has been implicated to play a central role [20,21]. The importance of Langerhans cells in the skin has also been indicated

[22]. On the other hand, nonspecific stimulation called "tape stripping" is known to induce inflammation in the skin; however, allergy-protective immune responses may be induced [23]. In addition, oral immunity tolerance was not induced in sterile mice [24]. Normal development of microbiome is believed to be necessary for the induction of food tolerance [25].

Thus, it is possible that the skin microbiome may be involved in inducing immune tolerance to EPIT. Although EPIT may be inferior to SCIT, SLIT, and OIT in terms of effectiveness, it is superior in terms of safety [26] and, hence, is expected to be clinically applied. Nevertheless, the optimum procedure has not yet been established. Presently, clinical research is being conducted using Viaskin® (DBV Technologies) [27]. However, various aspects of the treatment protocol remain to be determined, including the best pasting device and the specific methods, which need to be devised for individual patients. In the present study, we made use of a patch test device that is applied in general practice as an EPIT device. This is the first time that such a device has been used in EPIT, and one of the chief advantages of our method is that it can be implemented anywhere.

Regarding EPIT, numerous problems remain unresolved, including the selection of subjects, proper application site, pasting period, and method (including the pasting device), allergen selection, setting the appropriate dose, and long-term safety. Furthermore, the position of EPIT in the treatment of food allergies has not yet been determined, but various possibilities do exist. The technique could be used as an alternative therapy in cases where OIT is ineffective or difficult (e.g., abdominal symptoms are significant). In addition, the method could be applied as a bridging treatment for OIT. Furthermore, EPIT could be performed in combination with OIT, but the synergistic effects of this approach need to be ascertained.

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Author contributions

Koichi Yamaguchi and Shin Kawagoe designed the study and wrote the manuscript. Shin Kawagoe, Maiko Miyahara, Seigo Shirakawa, Makoto Nonoda and Kei Masuda contributed to data collection. Kota Hirai, Makoto Nonoda and Hiroyuki Mochizuki contributed to the data analysis and the preparation and revision of the manuscript. All authors read and approved the final manuscript.

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