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Safety and Effectiveness of Food Allergen Immunotherapy (Oral): A Systematic Literature Review and Meta-analysis

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ABSTRACT

Purpose: Food Allergen Immunotherapy (Oral) is a form of immunotherapy administered to patients who are allergic to foods such as egg, milk, and peanut. The food allergen is orally administered to the patient in an escalating dose for desensitization or tolerance development. The safety and effectiveness of the therapy were assessed using a systematic literature review and meta-analysis. Methods: For a literature search, 8 national databases and a number of international databases including Ovid-MEDLINE, Ovid-EMBASE, and Cochrane Library were used; and 13 articles (all from international databases) were selected. The target of Food Allergen Immunotherapy (Oral) included patients with food allergy, and the intervention was food allergen immunotherapy without limiting the food type. The safety and effectiveness of Food Allergen Immunotherapy (Oral) were assessed by reviewing all the articles reporting on the therapy. The control group received standard therapies including aversion therapy, no treatment, anti-histamine treatment, and placebo. Safety was assessed through the incidence of complication and emergency medication. Effectiveness was assessed based on therapy success rate, symptomatic improvement, and quality of life. Results: Although Food Allergen Immunotherapy (Oral) was shown to have successful desensitization in patients with food allergy, the safety of the technique has not yet reached an acceptable level; the possible reason is due to the high rate of complication and frequency of emergency medication. Also, each study employed varying protocols while relying on a small number of participants and a short monitoring period. Conclusion: The results of assessment suggest that the level of evidence from current literature review is low and further research is necessitated for the verification of the safety and effectiveness of the therapy (Grade of Recommendation: A; Level of Technology: II-b).

***Key words**: Allergen Immunotherapy, Review, Systematic, Meta-analysis, Food Hypersensitivity.*

1. INTRODUCTION

Food allergy is an immediate hypersensitivity to food proteins that is categorized as immediate hypersensitivity. It is reported in approximetely 8% of children under the age of 3 and within 2% of adults. Following the exposure to the allergen, the early-phase reactions such as increased vasopermeability, smooth muscle contraction, and increased mucosal secretion appear mostly within minutes; and the late-phase reactions may appear after several hours or within 1 or 2 days. Eosinophil chemotactic factor of anaphylaxis(ECF-A), Neutrophil chemotactic factor of anaphylaxis(NCF-A), platelete activating factor and cytokines cause the infiltration of neutrophils, eosinophils, and T helper 2 (Th2) cells that in turn causes massive tissue damage not only in the digestive system but also skin, respiratory system, and cardiovascular system. In severe cases, the condition may even lead to anaphylactic shock and death [1].

Potential allergens in the case of children include milk, egg, peanut, bean, and wheat; with the addition of fish, shell fish, and nuts (walnut, pine nut, chestnut) for adults. Thus, it is recommended that causal or high risk foods be thoroughly diagnosed and their intake be restricted [2]. At present, the only available therapy is the restricted diet although its impracticality and the lack of established intervention or nutrition data for developing immunotherapy or alternative diet, Because the treatment method is not established, it poses many problems in the clinical setting [1].

Among immunotherapies, the oral tolerance test involves repeated administration of the causal antigen to the patient through the digestive system so that future exposure to the same antigen will not incur aggressive immune responses [3].

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However, reports have been inconsistent for the mechanism, administration method, period and dose of immunosuppression by the antigen protein that is orally administered, indicating the need for further research to verify the safety and effectiveness of immunotherapy technique [1], [4], [5].

Thus, the present study aims to investigate, in an integrated manner, the safety and effectiveness of the technique Food Allergen Immunotherapy (Oral) that relies on the oral administration of food allergen in escalating dose for desensitization or tolerance development, by targeting patients with food allergy and performing a systematic literature review and meta-analysis.

2. MATERIALS AND METHODS

Systematic literature review was performed according to the reporting guidelines of the Arbitration Act Handbook as proposed by the Cochrane Union (Cochrane collaboration) and the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) group [6].

2.1 Literature search and data source

For literature search, 8 national databases (KoreaMed, National Library of Korea, National Assembly Library, KOLIS-NET, KERIS, KISS, KiSTi, and Korean Medical Database) and a number of international databases including Ovid-MEDLINE, Ovid-EMBASE, and Cochrane Library were used from January 1946 to March 2016, and was completed on March 18, 2016. The searching words were ‘‘(Hypersensitivity/) OR (hypersensitivity.mp.) OR Allergy.mp.’ AND ‘immunotherapy.mp. OR Immunotherapy/ OR ((immunologic OR oral) AND desensiti*).mp OR (specific oral tolerance induction.mp.) OR (oral AND (tolerance OR induction)).mp. OR Dose Response Relationship, Immunologic.mp. OR Dose-Response Relationship, Immunologic/ OR (OIT OR SLIT OR SOTI).mp.’. Two authors independently performed article selection, conding strategides and evaluation of the quality of studies with Scottish Intercollegiate Guidelines Network tool. An advisory council consisting of 8 specialists: 4 from pediatrics, 3 from allergy and clinical immunology, and 1 from family medicine, was formed; and council meetings were held for a comprehensive review of the searched articles.

We consulted the council for discussing the adequacy of search terms as well as the target patients, intervention technique, equivalent techniques for comparison, and appropriate medical outcomes, which formed the basis of determining what precautions to take for interpreting the selected articles. The discussions led us to decide the target to be the patients with food allergy; the intervention to be food allergen immunotherapy; the technique for comparison to be standard therapy (aversion therapy, no treatment, anti-histamine treatment) and placebo. With respect to medical outcomes, the assessment of safety was decided to be based on the incidence of complication and emergency medication; while the assessment of effectiveness was to be based on therapy success rate, symptomatic improvement, and quality of life. The selection criteria for the searched articles were i) studies where randomized clinical trials were performed; ii) studies targeting patients with food allergy; iii) studies where food allergen immunotherapy was investigated; iv) studies comparing the intervention technique with appropriate equivalent techniques; v) studies reporting at least one appropriate medical outcome.

2.2 Article quality evaluation

The article quality was evaluated using the ‘Methodology Checklist’ suggested in the Scottish Intercollegiate Guidelines Network (SIGN) [7], a tool developed in the U.K. The quality of the articles where randomized clinical trials did not employ an appropriate double-blind procedure for the target and the investigator or where the results were not standardized and measured by appropriate methods, was downgraded.

2.3 Statistical Analyses

Funnel plot was used to address publication bias. Sensitivity testing was also conducted to assess the magnitude of publication bias, which was determined using a fail-safe number, defined as the minimum number of patients with non-significant findings that are needed to overturn the conclusion of a meta-analysis. Larger fail-safe numbers indicate that the results are less prone to publication bias. For each outcome we tested the heterogeneity of results across the studies using “I^2”. If significant heterogeneity was observed ($p<.10$), a random effects model-which assigns a weight to each study based on individual study variance as well as between study variance-was used to pool the results together. Revman 5.0 Meta DiSc 1.4 version (Hospital Universtario Ramony Cajal, Madrid, Spain) was subsequently used for meta-analysis of the entire dataset. And we conducted research with statistical experts.

"Tolerance induction" and "desensitization" are different from each other strictly, but it is difficult to distinguish them from the literature, so we decided to analyze them through a specialist meeting (four pediatrics and three Allergy and Clinical Immunologist).

3. RESULTS

3.1 Article selection

The literature search produced a collection of 1,669 articles (0 from national databases; 1,666 from international databases; 3 from Cochrane Library). The articles obtained from the Cochrane Library were thoroughly reviewed by the advisory council in terms of the search databases of the previous systematic literature review, PICO, and exclusion criteria, in order to prevent any bias in the analysis results that may arise when articles of identical data source are included. As a result, it was found that the target of the previous systematic literature review deviated from the intervention, which led to the data extraction on the articles from the primary search after reviewing separate articles based on the exclusion criteria. Two reviewers independently followed the article selection criteria for the 1,370 articles (all from international databases) after having excluded the duplicated articles. When it was difficult to proceed with the article selection based solely on the abstract, more information on the corresponding articles

or their full texts were searched on the web. When a full text was not readily available on the web, the selection of the article was postponed until the full text was obtained. From the first phase of the article selection that was based on the abstract, 1,341 articles (97.9%) were excluded. From the second phase based on the availability of full text, 29 articles (0 from national databases; 29 from international databases) were selected. Two reviewers once again independently followed the article selection criteria, resulting in the exclusion of 16 articles. There was no conflict of opinions between the reviewers. In sum, 1,357 articles (99.1%) were excluded based on the selection criteria, leaving 13 articles (0.9%) for the final review. The agreement between the two reviewers (kappa) was 0.98.

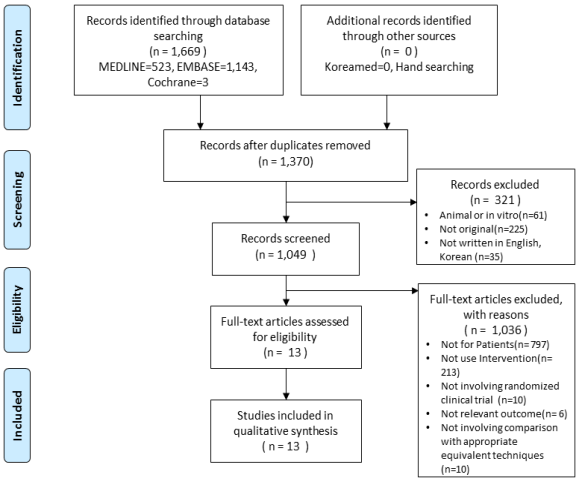

Fig. 1. Flow chart for article selection

3.2 Article quality evaluation result

The selected articles were 13 studies of randomized clinical trials. The article quality evaluation reported 1'++' in 4 articles [8]-[11], 1'+' in 8 articles [12]-[19], 1'−' in 1 article [20].

3.3 Study characteristics

The research type of all 13 selected articles was randomized controlled trial (RCT). Although the search had not limited the food type, intervention and control, only the food types of milk, egg, peanut, and apple were obtained from the search; and the selected articles included 6 on milk, 2 on peanut, 4 on egg, and 1 on apple.

3.4 Safety

Safety of Food Allergen Immunotherapy (Oral) was assessed through the incidence of complication and emergency medication. Thirteen articles reported on complication and 7 on emergency medication.

Among the 13 articles on the incidence of complication in the intervention group that received Food Allergen Immunotherapy (Oral), the mild complications (minor stomach pain, itchiness, runny nose, pink eye) were reported as 5.7%-85.7% in 12 articles; while the serious complications (severe laryngeal or bronchial spasm, anaphylactic shock) were reported as 7.4%-36.7% in 6 articles. In the control group that received standard therapy, the complications were reported as 14.3%-66.7% in 5 articles with the serious complications reported as 10.0%-31.3% in 3 articles.

For the incidence of emergency medication, the frequency of steroid injection in the intervention group was 20.0, 56.7% and that of histamine injection was 47.4%. The epinephrine injection was reported as 3.3%-30.8% in 6 articles. No incidence of drug injection occurred in the control group.

Table 1. Study characteristics

No.	Author (Nationality)	Year	Target (N, Age)	Intervention Period per phase, Dose (Location)	Control (Number, Age)	Monitoring Period	Level of Evidence
Milk							
1	Skripak (U.S)	2008	13, 9.3y	- Updosing: ≤20ml (hospital), - Maintenance: ≤500ml (home)	Placebo (7, 10.2y)	21W	++
2	Lee(Korea)	2013	14, 8.6y	- Updosing: ≤2ml (hospital), - Maintenance: 6 months, ≤200ml (home)	standard therapy(CM-free) (12,8.8y)	24W	+
3	Salmivesi (Finland)	2012	18, 9.8y	- Updosing: 2 weeks, ≤2ml (hospital), - Maintenance: ≤200ml (home)	standard therapy (oat milk, rice milk, soy milk) (10,9.8y)	25W	+
4	Martorell (Spain)	2010	30, 26m	- Updosing: ≤2.5ml (hospital), - Maintenance: ≤~200ml (home)	standard therapy(CM-free) (30,27m)	48W	+
5	Pajno (Italy)	2010	15, 9y	- Updosing: ≤200ml (home)	standard therapy(soy milk) (15, 10y)	18W	+
6	Longo (Italy)	2008	30, 7.9y	- Updosing: ≤20ml (hospital), - Maintenance: ≤150ml (home)	placebo(amino acid–based infant formula alone) (30, 8.1y)	48W	+
Peanut							
1	Anagnostou (U.K)	2014	49, −	- Updosing: 2, 5, 12.5, 25, 50, 100, 200, 400, 800mg/d (hospital) - Maintenance: 2~3 weeks (home)	standard therapy (aversion therapy) (50, −)	26W	++
2	Varshney (U.S)	2011	19, 84m	- Updosing: 0.1~6mg/ 30min (hospital) - Maintenance: q2w, total 400mg/1M (home)	placebo(oat) (19,69m)	48W	++
Egg							

No.	Author (Nationality)	Year	Target (N, Age)	Intervention Period per phase, Dose (Location)	Control (Number, Age)	Monitoring Period	Level of Evidence
1	Burks (U.S)	2012	40, 7y	- initial-day, ≤10 months (hospital) - build-up, 10~22 months (hospital) - maintenance phase, 22~24 months (hospital)	standard therapy (aversion therapy) (15, 7y)	96W	++
2	Dello (Italy)	2013	10, 6.6y	- Updosing: 0.015~5ml (hospital) - Maintenance: ≤40ml (home)	standard therapy (egg free) (10, 8.6y)	24W	+
3	Meglio (Italy)	2013	10, 8.4y	- Updosing: 0.27mg~13.6g (hospital) - Maintenance: ≤25ml (home)	standard therapy (aversion therapy) (10, 9y)	24W	+
4	Fuentes (Spain)	2013	40, 8.7y	- Updosing: 1~18ml (hospital) - Maintenance: ≤40ml (home)	standard therapy (aversion therapy) (32, 9.4y)	48W	−
Apple+Pollen							
1	Kopac (Switzerland)	2012	27, 36y	- Updosing: Small intake/2days (home) - Maintenance: 150~200g intake, target 128g (home)	No treatment (13, 42y)	32W	+

W, weeks; M, months;

Table 2. Complication of food allergen oral immunotherapy in analyzed studies

Author (Year)	Intervention, n (%)								Control, n (%)		
		Mild			Mod *		S †				
	N	stomach pain	Itchiness	runny nose + pink eye	stridor	Generalized itching	laryngeal+ bronchial spasm	shock	N	Mild	S †
Milk											
Skripak(2008)	13	5(38.5)	NM	NM	NM	NM	NM	7(53.8)	1	NM	NM
Lee (2013)	14	NM	12(85.7)	NM	NM	NM	NM	NM	12	0	NM
Salmivesi(2012)	18	2(11.1)	NM	NM	5(27.8)	NM	NM	NM	10	NM	1(10)
Martorell(2010)	30	NM	10(33.3)		14(46.7)		NM	2(6.7)	30	0	NM
Pajno (2010)	15	NM	NM	NM	NM	NM	3(20.0)		15	0	NM
Longo (2008)	30	14(46.7)	14 (46.7), labial/ 17 (15.8), oral	3(10.0)	NM	7(23.3)	11(36.7)	NM	30	0	NM
Peanut											
Ana-gnostou (2014)	49	0	NM	NM	NM	NM	NM	NM	50	0	NM
Varshney(2011)	19	NM	NM	NM	NM	NM	3(15.8)		9	NM	NM
Egg											
Burks (2012)	40		7 (17.5)		NM	NM	NM	NM	15	10(66.6)	NM
Dello (2013)	10		3 (5.7) - localized itching, sore, edema, rash		10 (18.9) - generalized itching, edema, sore, runny nose, rash		5 (9.4) - generalized symptoms and recurring nausea, bronchial spasm, frequent pulse, anxiety		10	3(60)	2(40)
Meglio (2013)	10				7 (70.0)				10	0	
Fuentes (2013)	40		6 (15.0) - stomach pain, itchiness, vomit		12 (30.0) - stomach pain, vomit		9 (22.5) - stomach pain, vomit, pink eye, runny nose		32	4(12.5)	10(31.2)
Apple											
Kopac(2012)	27	NM	NM	NM	NM	NM	2 (7.4)	NM	13	0	NM

*Mod, moderate; †S, severe; NM, no mention

Table 3. Emergency medication

Author (Year)	Food	Target	Intervention				Control	
			total	steroid	histamine	epinephrine	total	epinephrine
Skripak (2008)	milk	6-21y	13	-	-	4(30.8%)	7	0
Martorell (2010)	milk	24-30m	30	-	-	2(6.7%)	30	0
Pajno (2010)	milk	4-10y	15	-	-	2(13.3%)	15	0
Longo (2008)	milk	5-17y	30	17(56.7%)	-	1(3.3%)	30	0
Varshney (2011)	milk	1-16y	19	-	9(47.4%)	2(10.5%)	9	0
Dello (2013)	egg	5-11y	10	2(20.0%)	-	-	10	0
Fuentes (2013)	egg	4-15y	40	-	-	6(15.0%)	32	0

3.5 Effectiveness

Effectiveness of Food Allergen Immunotherapy (Oral) was assessed separately for each food type through immune-tolerance and quality of life.

For patients with milk allergy, 6 articles reported on immune-tolerance while no article reported on quality of life. The 6 articles on immune-tolerance targeted 222 patients; the proportion of immune-tolerant patients was 30.8%-90.0% in the intervention group and 23.3%, 66.7% in the control group that received standard therapy; and statistical significance varied across articles (p=.665, 002, <.001) with total risk ratio (RR) as 15.85(95% CI= 6.82~36.79, p<.001).

For patients with peanut allergy, 2 articles reported on immune-tolerance and 1 article reported on quality of life. The 2 articles on immune-tolerance targeted 127 patients; the proportion of immune-tolerant patients in the intervention group was 48.9% and 100%, respectively, and none in the control group (p<.001). In the article reporting on quality of life, both the intervention and the control groups showed improvement and there was significant intergroup difference (p<.001).

For patients with egg allergy, 4 articles reported on immune-tolerance while no article reported on quality of life. The 4 articles on immune-tolerance targeted 167 patients; 75.0%-90.0% of patients developed tolerance in the intervention group and 10.0%-21.9% of patients developed tolerance in the control group, with total RR as 11.45(95% CI= 2.26~58.07, p=.003).

For patients with apple allergy, 1 article reported on immune-tolerance while no article reported on quality of life. The article targeted 27 patients aged between 18-65; and 17 patients were shown to have developed immune-tolerance.

Table 4. Effectiveness of Food Allergen Immunotherapy (Oral)

Author (Year)	Target	Reference	Intervention, n (%) total	Intervention, n (%) immune-tolerant patient	Control, n (%) total	Control, n (%) immune-tolerant patient	p
Milk							
Skripak (2008)	6-2y	243ml	13	4 (30.8)	7	0	.002
Lee (2013)	below 16y	5ml	14	11 (78.6)	12	8 (66.7)	.665
Salmivesi (2012)	6-14y	200ml	18	14 (77.8)	8	0	-
Martorell (2010)	24-30m	200ml	30	27 (90.0)	30	7 (23.3)	-
Pajno (2010)	4-10y	200ml	15	10 (66.7)	15	0	-
Longo (2008)	5-17y	150ml	30	11 (36.7)	30	0	<.001
Peanut							
Anagnostou (2014)	7-16y	1,400mg	49	24 (48.9)	50	0	<.001
Varshney (2011)	1-16y	5,000mg	19	19 (100.0)	9	0	<.001
Egg							
Burks (2012)	5-18y	10g	40	30 (75.0)	15	0	.03
Dello (2013)	5-11y	40ml	10	0	10	0	
		10ml	10	9 (90.0)	10	1 (10.0)	
Meglio (2013)	above 4y	25ml	10	8 (80.0)	10	2 (20.0)	<.01
Fuentes (2013)	4-15y	10g	40	32 (80.0)	32	7 (21.9)	
Apple							
Kopac (2012)	18-65y	128g	27	17 (62.9)	13	0	<.001

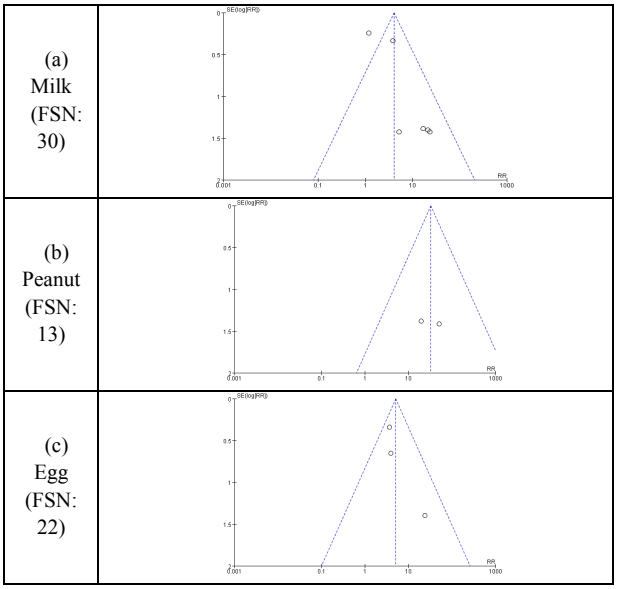

Fig. 2. Funnel plot of Food Allergen Immunotherapy

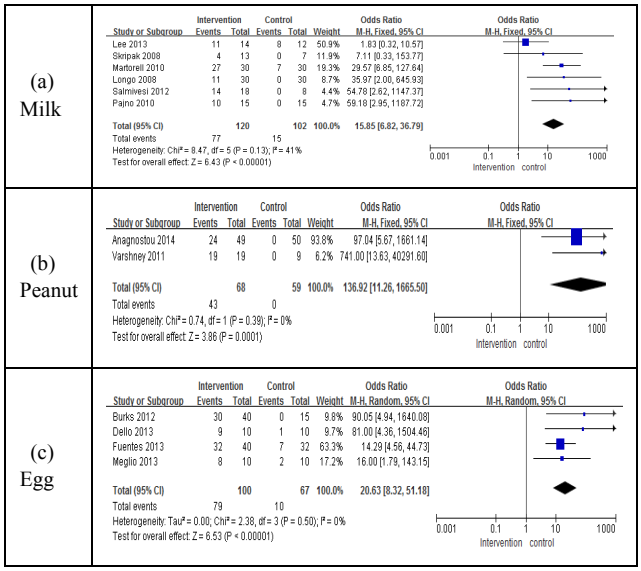

Fig. 3. Forest plot of Food Allergen Immunotherapy

4. DISCUSSION

The present study assessed the safety and effectiveness of Food Allergen Immunotherapy (Oral) that targets the patients with food allergy to whom the food allergen is orally administered in escalating dose for desensitization or tolerance development, by a systematic literature review and meta-analysis.

For safety, mild complications in the intervention group were reported in 12 out of 13 articles on the incidence of complication; and serious complications such as severe laryngeal or bronchial spasm and anaphylactic shock were reported in 6 articles. In the control group that received standard therapy, serious complications were reported in 3 articles. Furthermore, among the 7 articles on the incidence of emergency medication, epinephrine injection was reported as 3.4%-30.8% in 6 articles, whereas no drug injection was reported in the control group. Thus, the advisory council was of the opinion that, since the incidence of complication in the intervention group is higher than the control group that received standard therapy, and since the incidence of emergency medication is also high, the safety of Food Allergen Immunotherapy (Oral) is not yet clinically acceptable.

Effectiveness was assessed through therapy success rate, symptomatic improvement, and quality of life. Immune-tolerance against milk allergy was assessed based on 6 articles reporting on 224 patients. In the intervention group, 30.8~90.0% of patients developed tolerance whereas 23.3~66.7% of patients developed tolerance in the control group that received standard therapy. Statistical significance varied across articles with total risk ratio (RR) as 5.40. Immune-tolerance against peanut allergy was assessed based on 2 articles on 127 patients. Each article reported 48.9% and 100% of patients having developed tolerance in the intervention group whereas no successful case was reported in the control group ($p<.001$). Immune-tolerance against egg allergy was assessed based on 4 articles on 147 patients. 75.0~90.0% of patients developed tolerance in the intervention group and 10.0~21.9% of patients developed tolerance in the control group with total RR as 5.10. Immune-tolerance against apple allergy was reported in one article targeting 27 patients aged between 18~65, where 17 patients developed tolerance. For effectiveness, among the studies that targeted the patients with milk, peanut, or egg allergy, the proportion of patients who developed immune-tolerance and desensitization was higher in the intervention group than the control group that received standard therapy, with significantly high risk ratio indicating the positive effects of the intervention technique. However, the advisory council was of the opinion that, despite the desensitization effects from the intervention and the lack of alternative treatment other than the aversion therapy for patients with food allergy, there is a need for further research to verify the effectiveness of Food Allergen Immunotherapy (Oral) as different protocols were employed by each study while they relied on a small number of participants and a short monitoring period.

In conclusion, although Food Allergen Immunotherapy (Oral) was shown to have elicited successful desensitization in patients with food allergy, especially when there is no alternative treatment other than the aversion therapy, the safety of the technique has not yet reached an acceptable level considering the high incidence of complication or emergency medication, and the effectiveness requires further research since the studies varied in protocol and relied on a small number of participants and a short monitoring period. Thus, the advisory council stated that the current level of evidence from literature is low and further research should be performed to verify the safety and effectiveness of Food Allergen Immunotherapy (Oral) (Grade of Recommendation: A; Level of Technology: II-b).

At present, although immunotherapy is not a recommended treatment for patients with food allergy[20], there are numerous ongoing studies, and the findings of the present study indicated positive desensitization effects based on a systematic literature review. However, the tasks such as standardization of protocols have not been accomplished because of the general lack of interest and because each institution selectively applies the immunotherapy that suits their needs. Therefore, large-scale studies targeting domestic patients with food allergy should be performed as an effort to establish a diagnostic system that will enhance the quality of life of the patients.

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REFERENCES

[1] The Korean Academy of Asthma, *Allergy and Clinical Immunology*, Guideline for Consultation guide, 2012.

[2] S. Y. Lee, “Food allergy,” Korean Journal of Pediatrics, vol. 47, 2004, pp. 240-246.

[3] H. L. Weiner, A. Friedman, A. Miller, S. J. Khoury, A. al-Sabbagh, L. Santos, M. Sayegh, R. B. Nussenblatt, D. E. Trentham, and D. A. Hafler, “Oral tolerance: immunologic mechanisms and treatment of animal and human organ-specific autoimmune diseases by oral administration of autoantigens,” The Annual Review of Immunology, vol. 12, 1994, pp. 809-837.

[4] J. Fisherman-Lobell, A. Freidman, and H. L. Weiner, “Different kinetic patterns of cytokine gene expression in vivo in orally tolerant mice,” European Journal of Immunology, vol. 24, 1994, pp. 2720-2724.

[5] N. M. Tsuji, K. Mizumachi, and J. Kurisaki, “Interleukin-10 secreting Peyer's patch cells are responsible for active suppression in low-dose oral tolerance,” Immunology, vol. 103, 2001, pp. 458-464.

[6] D. Moher, A. Liberati, J. Tetzlaff, and D. G. Altman, “Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement,” Ann Intern Med, vol. 151, 2009, pp. 264-269.

[7] Scottish Intercollegiate Guidelines Network (SIGN), Available from URL: http://www.sign.ac.uk

[8] J. M. Skripak, S. D. Nash, H. Rowley, N. H. Brereton, S. Oh, R. G. Hamilton, E. C. Matsui, A. W. Burks, and R. A. Wood, "A randomized, double-blind, placebo controlled study of milk oral immunotherapy for cow's milk allergy," Journal of Allergy and Clinical Immunology, vol. 122, 2008, pp. 1154-1160.

[9] K. Anagnostou, S. Islam, Y. King, L. Foley, L. Pasea, S. Bond, C. Palmer, J. Deighton, P. Ewan, and A. Clark, "Assessing the efficacy of oral immunotherapy for the desensitisation of peanut allergy in children (STOP II): a phase 2 randomised controlled trial," Lancet, vol. 383, 2014, pp. 1297-1304.

[10] P. Varshney, S. Jones, A. M. Scurlock, T. T. Perry, A. Kemper, P. Steele, A. Hiegel, J. Kamilaris, S. Carlisle, X. Yue, M. Kulis, L. Pons, and B. Vickery, "A randomized controlled study of peanut oral immunotherapy: clinical desensitization and modulation of the allergic response," Journal of Allergy and Clinical Immunology, vol. 127, 2011, pp. 654-660.

[11] A. W. Burks, S. M. Jones, R. A. Wood, D. M. Fleischer, S. H. Sicherer, R. W. Lindblad, D. Stablein, A. K. Henning, B. P. Vickery, A. H. Liu, A. M. Scurlock, W. G. Shreffler, M. Plaut, and H. A. Sampson, "Consortium of Food Allergy Research (CoFAR). Oral immunotherapy for treatment of egg allergy in children." The New England Journal of Medicine, vol. 367, 2012, pp. 233-243.

[12] J. H. Lee, W. S. Kim, H. Kim, and Y. S. Hahn, "Increased cow's milk protein-specific IgG4 levels after oral desensitization in 7- to 12-month-old infants," Annals of Allergy, Asthma, & Immunology, vol. 111, 2013, pp. 523-528.

[13] S. Salmivesi, M. Korppi, M. J. Mäkelä, and M. Paassilta, "Milk oral immunotherapy is effective in school-aged children," Acta Paediatrica, 2012, epub ahead of print.

[14] A. Martorell, B. De La Hoz, M. Ibaez, J. Bone, A. Michavila, A. Plaza, E. Alonso, J. Garde, S. Nevot, L. Echevarria, C. Santana, and J. Cerda, "Specific oral tolerance induction (SOTI) as an useful treatment to cow milk proteins (CMPs) allergy," Allergy: European Journal of Allergy and Clinical Immunology, vol. 65, 2010, p. 371.

[15] G. B. Pajno, L. Caminiti, P. Ruggeri, R. De Luca, D. Vita, M. La Rosa, and G. Passalacqua, "Oral immunotherapy for cow's milk allergy with a weekly up-dosing regimen: a randomized singleblind controlled study," Annals of Allergy, Asthma, and Immunology, vol. 105, 2010, pp. 376-381.

[16] G. Longo, E. Barbi, I. Berti, R. Meneghetti, A. Pittalis, L. Ronfani, and A. Ventura, "Specific oral tolerance induction in children with very severe cow's milk-induced reactions," Journal of Allergy and Clinical Immunology, vol. 121, 2008, pp. 343-347.

[17] I. Dello Iacono, S. Tripodi, M. Calvani, V. Panetta, M. C. Verga, and S. Miceli Sopo, "Specific oral tolerance induction with raw hen's egg in children with very severe egg allergy: A randomized controlled trial," Pediatric Allergy and Immunology, vol. 24, 2013, pp. 66-74.

[18] P. Meglio, P. G. Giampietro, R. Carello, I. Gabriele, S. Avitabile, and E. Galli, "Oral food desensitization in children with IgEmediated hen's egg allergy:a new protocol with raw hen's egg," Pediatric Allergy and Immunology, vol. 24, 2013, pp. 75-83.

[19] P. Kopac, "Continuous apple consumption induces oral tolerance in birch-pollen-associated apple allergy," Allergy, vol. 67, 2012, pp. 280-285.

[20] V. Fuentes-Aparicio, A. Alvarez-Perea, S. Infante, L. Zapatero, A. D'Oleo, E. Alonso-Lebrero, "Specific oral tolerance induction in paediatric patients with persistent egg allergy," Allergologia et Immunopathologia (Madrid), vol. 41, 2013, pp. 143-150.

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