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CASE REPORT

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Tolerance induction for food allergy using immunoglobulin/histamine complex: A case report

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Abstract
Food allergy is defined as an immune-mediated adverse reaction to dietary proteins and is a major health problem with an increasing prevalence. Immunoglobulin/histamine complex (IHC) is an anti-allergy therapeutic that acts primarily by reducing histamine levels (histaminopexy). A 5-year-old male Korean patient with a food allergy was transferred for immunotherapy. Open food challenge (OFC) for wheat before treatment revealed positive reactions after challenge with 0.5g of wheat. Under a diagnosis of food allergy for wheat, allergic rhinitis, and atopic dermatitis, treatment with Histobulin™ (Green Cross PD, Korea), an IHC preparation, was initiated. After 23 injections, the patient did not exhibit any adverse reaction after the intake of 60 g of wheat in the OFC. Specific IgE levels and skin reactivities for wheat also decreased after IHC therapy. A 40-year-old female Korean patient presented with severe generalized urticaria, severe itching, and even whole body prickling immediately after every intake of shrimp or crab over 10 years; she also had allergic rhinitis. Basic allergy lab and skin prick testing results showed no abnormal findings, but OFC for shrimp and raw crab (both at 0.5 g) produced generalized urticaria, rashes, and itching immediately after intake. Under a diagnosis of chronic urticaria, allergic rhinitis, and food allergy to crab and shrimp, IHC therapy was initiated. After 86 injections of Histobulin™, the patient did not show any allergy reaction to shrimp or crab after the intake of 10 g of raw shrimp or 10 g of raw crab. IHC treatment successfully induced food allergen tolerance in a nonallergen-specific manner.

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Introduction

Food allergy is defined as an immune-mediated adverse reaction to otherwise harmless dietary proteins because of the failure of the immune system to develop tolerance after food protein exposure or establish oral tolerance.[1] Food allergy is a major health problem that affects 5–8% of young children and 2–4% of adults,[2] and the prevalence of food allergy is increasing in adult populations.[3] Furthermore, food allergen-specific IgE plays a central role in the pathogenesis, diagnosis, and management of food allergies of the immediate type.[4]

There is no complete cure for food allergy,[5] and currently, the standard of care is allergen avoidance, although the FDA has approved oral immunotherapy (OIT) for peanut allergy in the United States.[6] Allergen-specific OIT has been attempted for the definitive treatment of specific food allergies.[7]

Allergen-specific IgE and histamine play central roles in the pathogenesis of allergies, including food allergies; and H_1 receptor antagonists, known as H_1-antihistamines; and anti-IgE are used to manage food allergies.[1] H1 anti-histamines inactivate histamine H_1-receptor and thereby prevent the symptoms caused by histamine in allergic diseases such as food allergy, atopic dermatitis, pollinosis, and urticaria.[8] Anti-IgE monoclonal antibodies (such as Omalizumab), which sequester free IgE, have been investigated as either monotherapies[9] or in combination with OIT for the treatment of food allergy.[10]

Immunoglobulin/histamine complex (IHC) is an anti-allergy therapeutic, which acts mainly by histaminopexy.[11] IHC therapy has been used in allergic rhinitis, bronchial asthma, and chronic spontaneous urticaria (CSU),[12,13] which has also been treated with anti-histamine and Omalizumab.[14] In this context, IHC therapy may be considered a potential treatment for food allergy.

It was recently reported that during the treatment of Pfeiffer Weber-Christian disease with IHC therapy, multiple allergic diseases, including food allergy, resolved spontaneously.[15] However, the main focus of the report was the treatment of Pfeiffer Weber-Christian disease, and thus, no systematic scientific study was performed to evaluate the effects of IHC on food allergy.

In this case report, IHC therapy was tried in a patient with a crab and shrimp food allergy and CSU, and a patient with anaphylactic wheat allergy with allergic rhinitis and atopic dermatitis. Food allergy was confirmed by oral food challenge (OFC, a standard diagnostic process), and tolerance was achieved successfully in both cases after IHC therapy.

Case 1

A 5-year-old male Korean patient was transferred to the Department of Allergy and Clinical Immunology, Cheju Halla General Hospital, because of multiple food allergies for wheat, buckwheat, barley, eggs, peanut, walnut, and almond for immunotherapy from a private pediatric clinic. History taking revealed allergic reactions to soybean, wheat, eggs, and nuts, manifesting as vomiting, urticaria, and angioedema as anaphylaxis symptoms. At the time of his first visit, the patient was restricted to heated soybean products, such as soybean curd, and fermented soybean foods, such as soybean paste and fermented soybean sauce. In addition, he had been treated with a steroid ointment for atopic dermatitis and an anti-histamine for allergic rhinitis. There was no remarkable family history. Eczematous lesions on the trunk and buttocks were observed during a physical examination.

Laboratory tests were performed before and after treatment. Blood tests for allergic reaction evaluation were performed. These included a complete blood count with differential white blood cell analysis and tests for serum eosinophil cationic protein (ECP), serum total IgE, and IgE levels for specific allergens using a multiple allergen simultaneous test (MAST, Green Cross PD, Korea) before and after treatment. In the MAST test, the specific IgEs for 41 allergens were evaluated; results below 0.35 IU/mL were considered negative. In particular, specific IgE for wheat was measured using the UniCAP® (Pharmacia & Upjohn Diagnostics AB, Uppsala, Sweden) method.

Laboratory test-based allergy evaluation before treatment showed that total IgE and ECP were elevated at 588 IU/L (normal 350mIU/L>) and 48.6 ng/mL (normal 24 ng/mL>), respectively (Table 1A). The multiple allergen simultaneous test (MAST) was used to detect specific IgE levels for a wide range of allergens, including dust mites (Dermatophagoides pteronyssinus and Dermatophagoides farinae), various pollens (rye pollen, white oak, short ragweed, mugwort, Japanese hop, sweet vernal grass, Bermuda grass, orchard grass, Timothy grass, reed, sycamore, sallow willow, pine, Japanese cedar, acacia, dandelion, pigweed, redtop, bent grass, and Hinoki cypress), food allergens (wheat, egg white, soybean, maize, shrimp, peach, potato, and apple), and fungal allergens such as Alternaria alternata (Table 1B). In particular, specific IgE levels for wheat measured using UniCAP® were 23.0 IU/mL before treatment and 18.9 IU/mL after treatment. The skin prick test produced significant results for Dp, German cockroach, Bermuda grass, Timothy grass, and foods such as wheat, egg mix, almond, peanut, walnut, and peach (Table 1C). Skin reactivities to allergens including wheat also decreased after IHC therapy.

Food challenge remains the gold standard for the diagnosis of food allergy, and OFCs for wheat were performed before and after treatment using the protocol described in our previous report.[16] The patient was admitted to our institute for confirmatory oral challenge testing and to determine the minimal provocation dose for anaphylactic wheat allergy. Wheat was prepared in the form of noodles. The patient showed itching on the throat, dyspnea, cyanosis, and wheezing immediately after a 0.5 g wheat challenge. Wheezing was present during auscultation. Thus, anaphylactic food allergy to wheat was diagnosed before treatment.

IHC therapy was initiated under this diagnosis with suspected concomitant multiple food allergies, allergic rhinitis, and atopic dermatitis. Histobulin™ (Green Cross PD, Korea) was used as the IHC preparation. Histobulin™ is a histamine-fixed immunoglobulin preparation comprising 0.15 μg of histamine dihydrochloride and 12 mg of IgG in a 2 mL ampule.[17] Histaglobulin[12] and histaglobin[13] are generic names for Histobulin used in other countries and reports.

Table 1 The results of laboratory and skin prick tests. Class 6 100<, Class 5 50–100, Class 4 17.5–49.99, Class 3 3.5–17.49, Class 2 0.70–3.49, Class 1 0.35–0.69, and Class 0 0.35>. Wheal lengths were assessed as long or short. Histamine was used as a positive control, and normal saline was used as a negative control.

(A) Results of laboratory tests

	Before	After	Before	After	Unit	Normal Range
WBC	9.09	8.73	5.87	8.18	1,000/ul	3.5-10.0
Eosinophil	3.7	2.6	0.9	0.7	%	>5%
Basophil	0.6	0.3	0.7	0.4	%	1%>
ECP	48.6	17.6	16	14	ng/ml	Pediatric >19 Adult >24
Total IgE	588	496	17.5	15	IU/L	350>
IgA	136	111	250.5	235	mg/dl	27-195

(B) Allergen-specific IgE level by MAST

MAST	Case 1		Case 2		MAST	Case 1		Case 2	
	Before	After	Before 1	Before 2		Before	After	Before 1	Before 2
Dp	18.73	6.53	>0.35	>0.35	Bermuda grass	4.42	1.36	>0.35	>0.35
Df	8.02	13.42	>0.35	>0.35	Orchard grass	0.56	0.52	>0.35	>0.35
Cat	>0.35	>0.35	>0.35	>0.35	Timothy grass	3.1	1.23	>0.35	>0.35
Dog	>0.35	>0.35	>0.35	>0.35	Read	5.32	2.44	>0.35	>0.35
Egg white	36.42	19.11	>0.35	>0.35	Penicillium notatum	>0.35	>0.35	>0.35	>0.35
Milk	>0.35	>0.35	>0.35	>0.35					
Soybean	2.75	0.81	>0.35	>0.35	Syncamore	0.98	0.71	>0.35	>0.35
Maize	>0.35	0.47	>0.35	0.35	Sallow willow	0.66	1.01	>0.35	>0.35
Crab	>0.35	>0.35	>0.35	>0.35	Horse	>0.35	>0.35	>0.35	>0.35
Sesame	>0.35	0.6	>0.35	>0.35	Poplar mix	>0.35	>0.35	>0.35	>0.35
Shrimp	0.86	0.49	>0.35	>0.35	Guinea pig	>0.35	>0.35	>0.35	>0.35
Peach	28.43	6.51	>0.35	>0.35	Ash mix	>0.35	>0.35	>0.35	>0.35
Mackerel	>0.35	>0.35	>0.35	>0.35	Sheep	>0.35	>0.35	>0.35	>0.35
Rye Pollen	3.38	2.72	>0.35	>0.35	Pine	>0.35	1.46	>0.35	>0.35
Potato	7.88	4.23	>0.35	>0.35	Rabbit	>0.35	>0.35	>0.35	>0.35
Apple	9.27	5.3	>0.35	>0.35	Japanesse cedar	>0.35	0.68	>0.35	>0.35
Cockroach	0.35>	0.35>	0.35>	>0.35	Hamster	>0.35	>0.35	>0.35	>0.35
Cacao	0.35>	0.35>	0.35>	>0.35	Acacia	0.48	0.37	>0.35	>0.35
Cladosporium herbarium	>0.35	>0.35	>0.35	>0.35	Oxe Daisy	>0.35	0.61	>0.35	>0.35
					Dandelion	1.11	0.72	>0.35	>0.35
Aspergilus fumigatus	>0.35	>0.35	>0.35	>0.35	Golde rod	>0.35	>0.35	>0.35	>0.35
					Pigweed	1.41	0.72	>0.35	>0.35
Alternaria alternata	>0.35	11.93	>0.35>	>0.35	Redtop, bent grass	>0.35	>0.35	>0.35	0.35>
Birch-alder mix	>0.35	>0.35	>0.35	>0.35	Honey bee	>0.35	>0.35	>0.35	>0.35
Oak white	8.9	4.34	>0.35	>0.35	Yellow jacket	>0.35	>0.35	>0.35	>0.35
Ragweed short	1.99	1.14	>0.35	>0.35	Latex	>0.35	>0.35	>0.35	>0.35
Mugwort	1.97	0.95	>0.35	>0.35	Hinoki cypress	1	0.8	>0.35	>0.35
Japanese hop	1.16	0.95	>0.35	>0.35	English plantain	2.25	0.76	>0.35	>0.35
Hazelnut	>0.35	>0.35	0.35	>0.35	Acarus siro	>0.35	>0.35	>0.35	>0.35
Sweet vernal grass	6.74	0.85	>0.35	>0.35					

(continues)

An ampule of Histobulin™ was injected subcutaneously into the deltoid area of the upper arm every week. The clinical severity of atopic dermatitis was evaluated during treatment using the SCORad index, which has a total score of 103 points.[18] Written informed consent for the publication of this report was obtained from the child's parents, in accordance with the journal's patient consent policy. In both cases, food allergy was diagnosed just before the beginning of IHC therapy, and, in each patient, acquisition of tolerance to the allergenic food(s) was confirmed within 1 week after the final IHC treatment.

After four injections of Histobulin, the allergic rhinitis and urticaria development resolved. After 13 injections, he accidentally consumed eggs, but the resulting vomiting was

Table 1 Continued
(C) Results of skin prick testing

Skin Prick Test	Case 1		Case 2		Skin Prick Test	Case 1		Case 2	
	Before	After	Before	After		Before	After	Before	After
A Alternaria	0/0	7/7	0/0	0/0	Pork	0/0	0/0	0/0	0/0
A fumigatus,	0/0	0/0	0/0	0/0	Cod	0/0	0/0	0/0	0/0
A nigre	0/0	0/0	0/0	0/0	Oyster	0/0	0/0	0/0	0/0
Candida albicans	0/0	0/0	0/0	0/0	Salmon	0/0	0/0	0/0	0/0
Cladosporium	0/0	0/0	0/0	0/0	Prawn	0/0	0/0	0/0	0/0
P chrysogenum	0/0	0/0	0/0	0/0	Mackerel	0/0	0/0	0/0	0/0
German cockroach	7/4	0/0	0/0	0/0	Tuna	0/0	0/0	0/0	0/0
Dp	4/4	6/6	0/0	0/0	Almond	4/4	0/0	0/0	0/0
Df	0/0	0/0	0/0	0/0	Peanut	6/4	0/0	0/0	0/0
Dog	0/0	0/0	0/0	0/0	Bean	0/0	0/0	0/0	0/0
Cat	0/0	0/0	0/0	0/0	Carrot	0/0	0/0	0/0	0/0
Grey elder/silver birch	0/0	0/0	0/0	0/0	Cabbage	0/0	0/0	0/0	0/0
Grass mix	0/0	0/0	0/0	0/0	Walnut	4/5	0/0	0/0	0/0
Mugwort	0/0	0/0	0/0	0/0	Maize	0/0	0/0	0/0	0/0
Short ragweed	0/0	0/0	0/0	0/0	Peach	10/4	0/0	0/0	0/0
Black willow pollen	0/0	0/0	0/0	0/0	Tomato	0/0	0/0	0/0	0/0
Orchard grass	0/0	0/0	0/0	0/0	Black pepper	0/0	0/0	0/0	0/0
Bermuda grass	4/4	0/0	0/0	0/0	Spinach	0/0	0/0	0/0	0/0
Timothy	4/4	0/0	0/0	0/0	Wheat flour	5/4	0/0	0/0	0/0
English plantain	0/0	0/0	0/0	0/0	Rabbit	0/0	0/0	0/0	0/0
English Rye grass	0/0	0/0	0/0	0/0	Kapok	0/0	0/0	0/0	0/0
Holm oak	0/0	0/0	0/0	0/0	Hop	0/0	0/0	0/0	0/0
Japanese cedar	0/0	0/0	0/0	0/0	F acacia	0/0	0/0	0/0	0/0
Cotton flock	0/0	0/0	0/0	0/0	Pine	0/0	0/0	0/0	0/0
Milk mix	0/0	0/0	0/0	0/0	Poplar.	0/0	0/0	0/0	0/0
Egg mix	8/6	7/7	0/0	0/0	Histamine	5/5	6/5	4/5	5/5
Chicken	0/0	0/0	0/0	0/0	Normal Saline	0/0	0/0	0/0	0/0
Beef	0/0	0/0	0/0	0/0					

reduced. After 14 injections, the clinical severity of atopic dermatitis began to improve markedly (Figure 1A). After 22 injections, no adverse reaction occurred after the accidental intake of almonds and wheat. Thus, after 23 injections, an OFC test for wheat revealed no adverse reaction after the intake of 60 g of wheat. Thus, the patient achieved allergy tolerance for wheat after treatment and showed no clinical manifestations of food allergy after eating foods containing wheat without restriction over a period of 4 years.

Case 2

A 40-year-old female Korean patient visited the Department of Allergy and Clinical Immunology, Cheju Halla General Hospital, because of continued severe urticaria and itching on her entire body for 6 months. The patient stated that symptom intensity was increasing, generalized urticaria developed daily, and she was taking anti-histamine daily. In addition, she reported angioedema developed on her face, respiratory difficulties, including chest tightness after intake of shrimp and crab, and two emergency room visits over the previous 6 months. The patient had severe generalized urticaria and experienced severe itching and even prickling over her whole body immediately after eating shrimps or crab for last 10 years. She also had allergic rhinitis. Her medical history included the development of Graves' disease some 10 years ago at the same time when food allergy and urticaria developed. She continued to receive treatment for Graves' disease. There was no other relevant family history.

Basic blood tests were performed for the allergic evaluation (Table 1A). Laboratory tests produced no abnormal result. White blood cell (WBC) count was 5.87 (1000/ul), eosinophil and basophil fraction in WBC were 0.9% (normal range, 0–5%) and 0.7 % (normal range, 0-1%), respectively. Blood ECP level was 16.00 ng/mL (normal range, 24 ng/mL >=). Serum total IgE level was 17.5 IU/mL (normal range, 350 IU/mL>). MAST testing failed to identify any item with a high specific IgE level (Table 1B). Specific IgE testing, especially for shrimp and crab, performed using UniCAP (Pharmacia & Upjohn Diagnostics AB, Uppsala, Sweden) for the evaluation of shrimp and crab allergy was negative at 0.13 IU/mL (Class 0) for shrimp and 0.10 IU/mL for crab. Skin prick testing results are negative before and after treatment (Table 1C).

OFCs for shrimp and crab were performed before treatment. Before treatment, the patient showed generalized urticaria, rashes, and itching after raw crab 0.5 g or shrimp

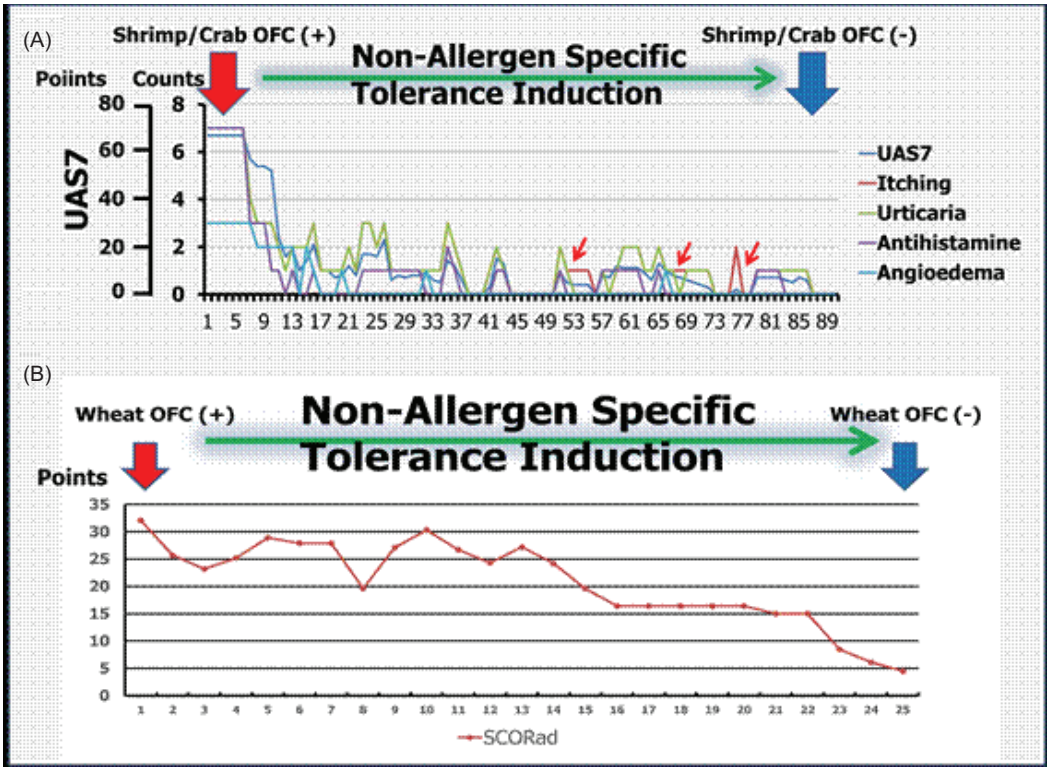

Figure 1 (A) Clinical progress of Case 1. Clinical severity of atopic dermatitis was monitored using SCORad indices, and anaphylactic food allergy was confirmed by OFC before and after immunoglobulin/histamine complex (IHC) therapy. After IHC therapy, wheat was administered, and tolerance was achieved with improvements in atopic dermatitis and allergic rhinitis. (B) Clinical progress of Case 2. Clinical severity was monitored by UAS7 (urticaria activity scoring for 7 days). Clinical severity was improved with gradually decreasing weekly counts of itching, urticaria, medication, and angioedema. OFC for food allergy was performed before and after IHC therapy. Shrimp and crab allergies were present before treatment, and tolerance was achieved by IHC therapy and confirmed by OFC.

0.5 g challenge immediately after intake. Accordingly, food allergy for shrimp and crab was diagnosed.

IHC therapy was initiated under a diagnosis of chronic urticaria, allergic rhinitis, and food allergy for crab and shrimp. Histobulin™ (Green Cross PD, Korea) was used as the IHC preparation, and also an ampule of Histobulin™ was injected subcutaneously into the deltoid area of the upper arm weekly. The clinical severity of CSU was evaluated at every treatment using the Urticaria Severity Score developed by Jariwala et al.; the total score was 92 points.[19]

After five injections, the clinical severity of CSU began to improve (Figure 1B). After 12 injections, clinical manifestations fluctuated at around mild severity, and after 39 injections, the patient intermittently experienced a symptom-free status. After 86 injections, a symptom-free status was maintained over 4 weeks, indicating the clinical remission of CSU. An OFC for shrimp and crab conducted at the time showed no adverse reaction after the intake of 10 g of raw shrimp and 10 g of raw crab, indicating the acquisition of complete allergy tolerance to shrimp and crab. After treatment, the patient did not experience any of the clinical manifestations of CSU, and at her last visit 4 years after treatment commencement, the patient reported freely eating foods containing shrimp and crab without any problem.

Discussion and Conclusions

Nonallergen-specific IHC therapy successfully induced tolerance for shrimp and crab in a case and for wheat in the other case. Classically, desensitization or tolerance for specific allergens in allergic diseases has been generally achieved using repetitive allergenic challenges with increasing allergen doses as exemplified by allergen-specific sublingual immunotherapy,[20] subcutaneous immunotherapy,[21] and OIT.[22] In particular, for food allergies, OIT has been performed with limited success.[23] In a previous report, IFN-γ was successfully used as an adjuvant to achieve tolerance for food allergy.[24]

The therapeutic concept used in the described cases was nonallergen-specific immunotherapy without allergenic desensitization, which stemmed from the concept of polydesensitization as coined by Mottard in 1990.[25] The concept of "non-specific immunotherapy" was also described in 2001 when anti-IgE therapy was also utilized to improve polydesensitization,[26] and this technique was utilized by us as an adjunct to IFN-γ therapy for atopic dermatitis.[27] In this previous report, IFN-γ therapy reduced total IgE levels and specific IgE levels for multiple allergens, and in a recent report, it was also reported that allergen-specific IgE levels and total IgE levels were

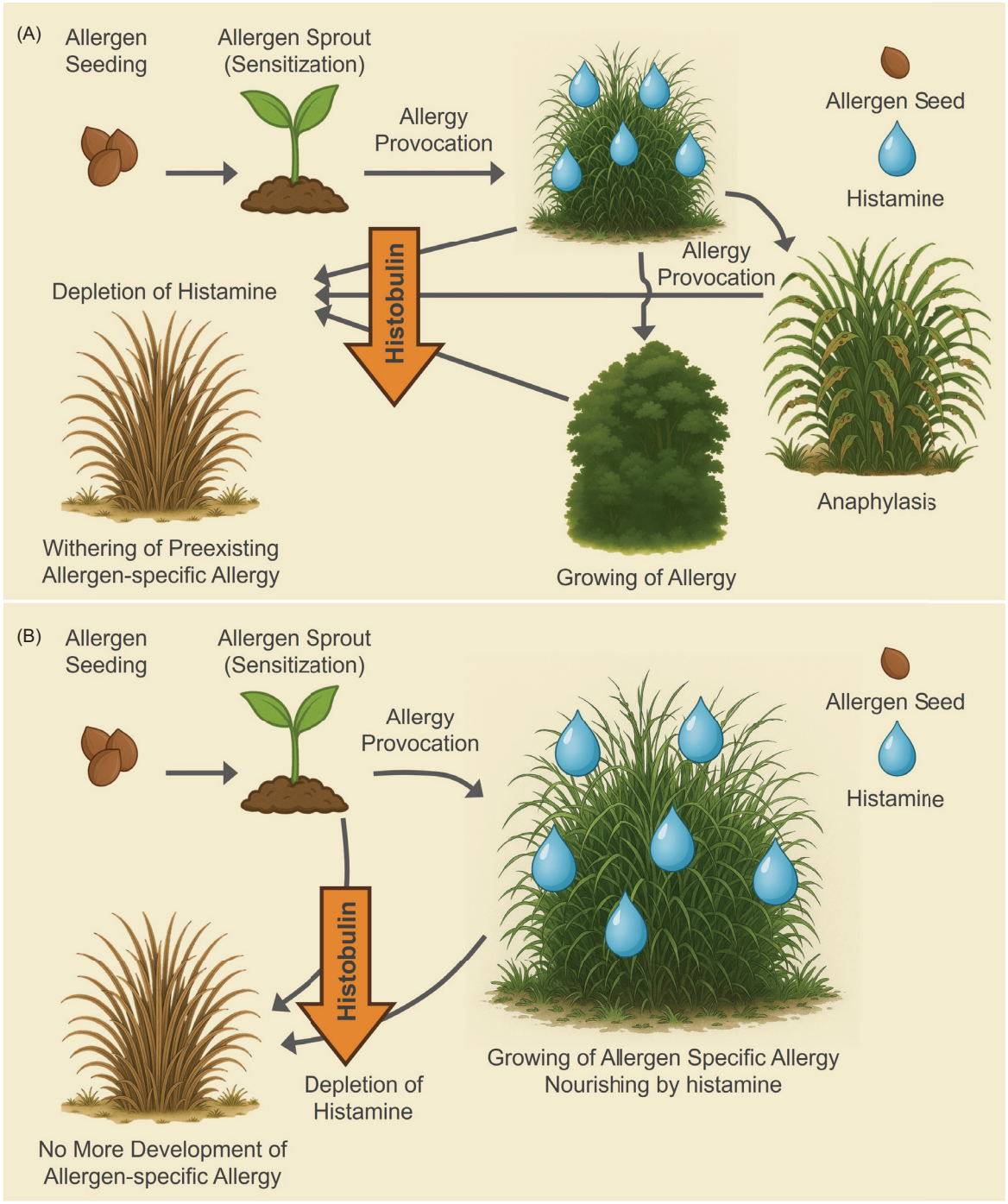

Figure 2 Histamine nourishing theory. Histobulin™ (Green Cross PD, Korea) was used as the immunoglobulin/histamine complex (IHC) preparation. (A) Theory for the action mechanisms of IHC in allergy. Allergen-specific allergy begins in a minor way and then develops because of persistent allergen challenge to become allergic disease or even anaphylaxis. During this process, histamine plays a role as a mediator and nutrient for the growth of preexisting allergen-specific allergy. However, IHC causes a long-term reduction in histamine levels, which causes a withering of preexisting allergen-specific allergies. (B) Prevention of further development of allergen-specific allergy by Histobulin. Depletion of histamine also prevents further development of additional allergen-specific allergy.

decreased by IHC therapy,[15] and multiple allergic diseases were resolved simultaneously, including crab and shrimp food allergy without a standard diagnostic procedure. This report suggested the use of IHC for the treatment of non-allergen-specific immunotherapy for food allergy. Here, we report that IHC therapy in a nonallergen-specific manner resulted in the successful induction of tolerance for food allergy in two cases of food allergy.

The most important feature of this immunotherapy is its nonallergen-specific manner, which means it is much

safer than allergen-specific immunotherapy, which can result in untoward reactions because of allergenic challenges, such as anaphylaxis with respiratory difficulty.[25] We surmise that the concept of nonallergen-specific immunotherapy might be expanded to the induction of tolerance in cases of drug allergy. However, IHC therapy for tolerance induction is limited because it is difficult to determine whether a patient has become tolerant of an allergenic food, as allergenic challenges are not performed during treatment. In allergen-specific immunotherapy, the acquisition of tolerance is easily evaluated because patients exhibit clinical symptoms and signs after every challenge.[25] Thus, additional studies, including those on the duration of treatment, drug dose, and the exact treatment protocol, such as how to confirm acquisition of tolerance and when to stop treatment, are required to establish clinical protocols.

Interestingly, IgEs specific for shrimp and crab were negative in Case 2 in spite of the patient showing strong clinical allergic reactions. The current trend for diagnosing IgE-mediated food allergy is toward the quantitative analysis of specific IgEs for allergenic foods.[24] However, Case 2 shows that laboratory results for allergen-specific IgE are diagnostically complementary and not confirmatory. We emphasized that patients negative for allergen-specific IgE may exhibit allergic reactions, and patients with a high allergen-specific IgE titer may not do so when challenged with an allergenic food. Thus, IgE-mediated food allergy patients found to be negative for allergen-specific IgE should be viewed cautiously because it is unpredictable whether such patients will react to the allergen. As mentioned previously, the only confirmatory diagnostic test for food allergy is OFC.[16]

In Case 2, tolerance for shrimp and crab was achieved simultaneously with the resolution of CSU and allergic rhinitis, which is reminiscent of a previous report in which atopic dermatitis and allergic rhinitis were resolved simultaneously by IHC therapy.[15] Furthermore, IHC also induced complete remission of CSU in a recent report.[28] The mechanisms of allergen-specific desensitization or tolerance induction are explained as allergen-specific immunological changes caused by repeated allergen challenge and include the induction of allergen-specific IgG4,[29] allergen-specific regulatory T cells,[30] and allergen-specific regulatory B cells.[31] Although the immunologic action mechanism of IHC-based treatment in CSU is unresolved, it is probably best understood as acquired tolerance to internal or self-allergens, which play important roles in the immunopathogenesis of CSU. Interestingly, adjuvant omalizumab decreased the time required to reach the maintenance dose for OIT, but the single and/or direct effect of omalizumab on desensitization or tolerance induction for allergens has not been determined.[32, 33] Currently, IHC and IFN-γ are pharmaceuticals with polydesensitization effects, and IHC appears to be a biosimilar therapeutic for nonallergen-specific immunotherapy.

Histamine plays various vital immunological and biological roles in man.[34] Normal plasma histamine levels are 37±17 ng/mL, and in those with a food allergy are 37±15 ng/mL when symptom-free and 57±34 ng/mL during an asthmatic attack.[35] Atopic children have higher plasma histamine levels than normal children. Furthermore, plasma histamine levels are positively related to the severity of atopic disease.[36] Also, normal histamine levels were reported to be higher in older.

Histaminopexy was first described in 1964.[37] IHC was developed for histaminopexy effects, and reductions in histamine levels are the major effect of IHC.[11,12] Anti-histamine antibody was reported to be induced by IHC and plays an important role in histaminopexy.[38] Furthermore, IHC therapy changes response to histaminopexy, and these changes seem to be maintained.[39] With persistent reductions in histamine levels, allergic status seems to be improved with improving allergen-specific allergy in a nonallergen-specific manner.

An allergy is an immunologic response to an allergen and not to an invasion by a foreign body. The human body must maintain an allergic status for defense purposes, and IgE has been demonstrated to have a short serum half-life of approximately 2.5 days and the lowest synthesis rate and highest fractional catabolic rate of the five major classes of immunoglobulins.[40] However, high IgE levels lead to lower relative antibody catabolism, resulting in a half-life increase from 1.8 to 5.8 days.[41] Histamine has been posited to act as a nutrient for the maintenance of allergic status, and a persistent reduction in systemic histamine seems to reduce allergic status and allergen-specific allergies nonspecifically. Allergies are maintained by a supply of histamine that exceeds normal levels.

Allergens are the triggers of allergen-specific allergies (Figure 2). These allergies are minor effects at first but develop on exposure to a persistent allergen challenge to become allergic diseases or even anaphylaxis with the development of allergen-specific allergy. During this process, allergic tension is maintained by histamine as a mediator and nutrient for the growth of allergen-specific allergies. At high histamine levels, the human body recognizes an allergen challenge as a foreign body invasion, and to meet such challenges, anti-allergen capacity is increased using histamine. On the other hand, IHC therapy causes a continued reduction in histamine levels, and the immune system interprets this as the absence of a foreign body attack. Thus, continued reduction in histamine level by IHC appears to reduce the systemic expectation of foreign body invasion and cause a switch from the Th2 dominant status to a Th1/Th2 balanced status.[42] This hypothesis also seems to be applicable to internal allergens, which have been identified as causes of CSU, and would explain why IHC therapy induced complete CSU remission.

There are four histamine receptors (H1, H2, H3, and H4)[43] distributed throughout the body, and through these receptors, histamine acts as an important neurotransmitter. However, excessive histamine production caused by allergy provocation is pathologic and induces many kinds of allergic diseases, including anaphylaxis. Characteristically, Ag-Ab response maintains Ag-Ab balance and prevents histamine from being completely removed from the circulation. So, IHC therapy appears to control histamine levels at normal levels and prevent excessive levels associated with an allergic status.

The action mechanism of nonallergen-specific immunotherapy seems to be quite different from that of allergen-specific immunotherapy. Interestingly, IHC may result in the simultaneous toleration of multiple allergens and the

resolution of multiple allergic diseases. Based on our experiences and several previous reports, reductions in histamine levels by IHC therapy decrease allergen-specific IgE and skin reactivity to allergens, as determined by the skin prick test (Table 1). It would appear that allergen-specific allergies are not maintained when the enough supply of histamine is reduced (Figure 2).

In this report, IHC treatment, a nonallergen-specific immunotherapy, successfully induced food allergy tolerance and simultaneously resolved multiple allergic diseases, and it is suggested that a histamine-nourishing theory (Figure 2) was suggested as the underlying mechanism of IHC immunotherapy, which might be responsible for tolerance induction by IHC and further investigations may be needed.

Conclusions

This is the first report indicating the fact that IHC-based treatment successfully induced food allergen tolerance in a nonallergen-specific manner. We propose a histamine-nourishing theory as a potential mechanism underlying IHC immunotherapy. The optimal dosage, duration of applicaion, and treatment protocol should be defined in further studies.

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Mandatory Disclosure on Use of Artificial Intelligence

The authors declare that no AI-assisted tools were used in the preparation of this manuscript. All references have been manually verified for accuracy and relevance.

Author Contributions

All authors contributed equally to this article.

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this manuscript.

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