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ORIGINAL ARTICLE

Rush Specific Oral Tolerance Induction in School-Age Children with Severe Egg Allergy: One Year Follow Up

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ABSTRACT

Background: At present, the only treatment for food allergy is to avoid the allergy-causing food. Some trials of specific oral tolerance induction (SOTI) have been carried out, but the rate of tolerance induction was low despite long treatment periods, at least 3 months to several years. A new type of treatment is long desired. The objectives of this study are to perform our rush SOTI for school-age patients with severe egg allergy, and to evaluate the safety and efficacy of this method for one year.

Methods: Six school-age children (7-12 years of age) with severe IgE-mediated egg allergy confirmed by double-blind, placebo-controlled food challenge (DBPCFC) underwent rush SOTI, in which patients ingested increasing doses of egg several times every day. After rush SOTI, patients ingested the maintenance dose of egg at least twice a week.

Results: In DBPCFC, the median threshold dose of egg white inducing allergic reactions was 0.152 g (0.012-0.360 g). All subjects acquired tolerance to more than one whole egg (60 g). It took only 12 days (9-18 days). None experienced any serious reaction. We observed a decrease in IL-10 and an increase in TGF-β1 at 6 months and a decrease in egg-specific IgE and an increase in egg white-specific IgG_4 at 12 months after rush SOTI in blood. All subjects have been able to ingest more than one whole egg ever since.

Conclusions: Our rush SOTI is a safe and effective treatment for severe food allergy since only a few weeks are needed to acquire tolerance. It would replace allergen avoidance as the treatment for food allergy.

KEY WORDS

egg allergy, food allergy, immunotherapy, oral tolerance, rush

INTRODUCTION

Egg allergy is the most common food allergy in Japanese children, affecting about 1 to 5% of young children in prevalence, especially in immediate hypersensitivity reactions.[1] It can cause severe allergic reactions in sensitized children.[2,3] Although two thirds of the children with egg allergy will outgrow their condition by the age of 6 years, most school-age patients who have not developed tolerance by that age have egg allergy for a long time.[4,5]

At present, the only treatment for food allergy is the hope of outgrowing the food allergy while on an allergen avoidance diet and education in case of accidental ingestion of the causative food.[6] However, strict allergen avoidance can cause significant dietary limitations. Previous studies have found that patients with food allergy and their families have a significantly reduced health-related quality of life.[7,8] The fear of unexpected and life-threatening reactions has a very negative effect. Injection immunotherapy has proven unsafe in food allergy[9-12]; in addition, anti-IgE therapy is expensive and will not change the natural history of allergic disease.[13] In recent years, some tri-

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Table 1 Rush SOTI protocol

Rush SOTI	To ingest egg 3-5 times a day at 30-minute intervals.
Initial dose	Start approximately at a tenth of the threshold dose determined at DBPCFC for each patient.
Materials and increase in dose	Start with powdered egg white, the dose is increased approximately 1.2 fold every time.
	When reaching 1,000 mg of powdered egg white, the material is changed to 8 g of heated egg (scrambled egg), and the dose is increased 1.5 fold every time up to 60 g.
	If mild symptoms develop, the same dose or the previously tolerated dose is repeated.
	If the symptoms are significant, rush SOTI is stopped.
Maintenance	To ingest the maintenance dose of egg at least twice a week for maintenance.
Challenge test	Perform oral challenge test with 1 g of powdered egg at 9-12 months after starting maintenance.

als of specific oral tolerance induction (SOTI) in food allergy have been carried out, but the rate of induction of tolerance was low despite long treatment periods and most of the subjects were very young children, which made it difficult to differentiate actual effects of the treatment from natural outgrowth.[14-20] Thus, a new type of safe and effective treatment is eagerly desired.

Patients who react to aeroallergens can choose active forms of treatment either through medication or allergen specific immunotherapy. Allergen specific immunotherapy induces tolerance to allergens, and it can change the natural history of the disease.[21,22] Rush injection of aeroallergen immunotherapy has been performed in our hospital for more than 10 years for children. On the basis of our experiences and prior studies, we realized rush immunotherapy was very effective, because it allowed injection of a high dose of the allergen in a short period.[23,24] Therefore, we thought that rush SOTI might induce tolerance better in patients with food-allergy during a short period, and we prepared our rush SOTI protocol. In our protocol, the real threshold doses of egg at which symptoms became evident were determined by a double-blind, placebo-controlled food challenge (DBPCFC) in all patients just before rush SOTI. So we could clearly elucidate the changes of doses that patients could tolerate in short periods during rush SOTI.

METHODS

PATIENT SELECTION

We included school-age children with food allergy to hen's egg who had high levels of egg white-specific IgE and a history of at least 1 severe allergic reaction (i.e., reactions defined as grade 4 and 5 according to the grading of food-induced anaphylaxis in Sampson's paper[25]) after accidental ingestion of small amounts of heated egg (less than 2 g) requiring emergency treatment within 1 year before the treatment. This study protocol was approved by the Institutional Review Board. Written informed consent was obtained in accordance with the institution's ethics guidelines for research in children.

RUSH SOTI PROTOCOL

All subjects were hospitalized during all processes of DBPCFC to the end of rush SOTI. Intramuscular adrenaline, oral and intravenous antihistaminics, oxygen, and bronchodilator for inhalation were ready to be used at the bedside at all times.

DBPCFC:

We performed DBPCFC to confirm egg allergy. It was carried out by administering placebo or powdered hen's egg white, "Dried egg white K type", a product of Q.P. Egg Corporation (Tokyo, Japan), doubling the dose every 20 minutes. Not to confuse psychological or mental reactions with a true positive reaction in DBPCFC, only significant and objective symptoms were considered to be positive allergic reactions as described by Niggemann and Beyer.[26] A single episode of vomiting was not taken as a positive reaction, while severe and repetitive vomiting was recognized as positive. If the DBPCFC was not positive, the patient was excluded.

Because the last dose of DBPCFC performed in a mode mentioned above was not always the real threshold for each subject, we repeated the challenge test at the interval of 1 to 2 hours to determine the real threshold dose until symptoms became evident. Then, we started rush SOTI.

Rush SOTI:

Table 1 summarizes our rush SOTI protocol. The initial dose of powdered hen's egg white for each patient was set at approximately one tenth of the threshold dose for that patient. After the initial dose, the next and subsequent doses were increased approximately 1.2 times every time and administered every 30 minutes 3 to 5 times in one day or until the patient developed a positive reaction. Powdered egg was mixed with an acceptable vehicle food chosen by the subject. When the dose reached 1 g of powdered egg, which was equivalent to 8 g of real raw egg white, we changed the material to heated egg starting at 8 g. Scrambled egg heated at 70 to 82°C for 10 seconds was used, because the powdered egg was not suitable

for subjects to keep eating large dose everyday due to its taste, and the aim of this therapy was to help subjects to eat dishes and confectionery containing heated egg in daily life. Thereafter, doses were increased by approximately 1.5 times every time.

All patients were sent home every Saturday, Sunday and holiday for refreshment. To keep the effect of rush SOTI, they were given the highest previously tolerated dose, which was not increased at home, three times a day in at least 1-hour intervals. We educated all caregivers about the nature of possible reactions due to food allergy and the medical measures.

The goal of rush SOTI was one whole egg (about 60 g). If the subject reacted to one of the doses during the course of rush SOTI and symptoms were mild, then that dose or the previously tolerated dose was repeated, and rush SOTI protocol proceeded. But if severe adverse reactions such as anaphylaxis of grade 5,[25] marked dyspnea or cyanosis developed once, or milder reactions were observed 3 times at the same dose, the increase in dose of egg was abandoned. After taking the highest dose for 3 consecutive days without developing any allergic reactions, the rush SOTI was finished and that dose was chosen as the maintenance dose.

Maintenance:

The subjects were discharged and instructed to ingest the maintenance dose of egg at least twice a week at home to keep the effect of rush SOTI. Regular follow-up visits were planned.

EGG-SPECIFIC IgE, IgG4, HISTAMINE RELEASE TEST, T HELPER 1/T HELPER 2 RATIO, AND CYTOKINE CONCENTRATIONS

Blood samples were collected just before DBPCFC, on the last day of rush SOTI and at 3, 6 and 12 months after starting maintenance. They were analyzed for egg white-specific serum IgE, ovomucoid-specific serum IgE, egg white-specific serum IgG4, histamine release test of egg white, T helper 1/T helper 2 ratio, and cytokines. Egg white-specific IgE and ovomucoid-specific IgE were quantified using the Phadia CAP System FEIA (Phadia, Uppsala, Sweden). Egg white-specific IgG4 was quantified using the original ELISA system of SRL (SRL Inc., Tokyo, Japan), whose measuring range is 25-800 U/mL. Histamine release test of egg white was quantified using "HRT Shionogi" (Shionogi, Osaka, Japan).[27] T helper 1 (Th1, IFN-γ+/IL-4-/CD4)/T helper 2 (Th2, IFN-γ-/IL-4+/CD4) ratio assayed by the flow cytometry of SRL (SRL Inc.).[28] Serum IL-4, IL-10, and IFN-γ were quantified using the original CLEIA system of SRL (SRL Inc.), the Human IL-10 Ultra Sensitive ELISA Kit (BioSource International, Camarillo, CA, USA), and the Human IFN-γ ELISA (Bender MedSystems, Vienna, Austria). Plasma TGF-β1 was quantified using the Quantikine Human TGF-β1 Immunoassay Kit (R&D Systems, Minneapolis, MN, USA).

SKIN PRICK TEST

Skin prick test for egg-white was performed just before DBPCFC, on the last day of rush SOTI and at 3, 6 and 12 months after starting maintenance, using "Allergen extracts for scratch test" (Torii Pharmaceutical, Tokyo, Japan).

CHALLENGE OF POWDERED EGG DURING MAINTENANCE PERIOD

We performed oral challenge test with 1 g of powdered egg at 9 to 12 months after starting maintenance.

STATISTICAL ANALYSIS

Wilcoxon signed-rank sum test (2-tailed, $P < 0.05$) was used to evaluate the changes in IgE, IgG4, histamine release test, Th1/Th2 ratio, cytokine levels, and the wheal size after the skin prick test.

RESULTS

SUBJECTS

Six subjects were initially enrolled. All of 6 subjects had positive reactions in DBPCFC, and all patients completed the study. Table 2 outlines patient characteristics. There were 4 boys and 2 girls, the median age was 9.7 years at the start of the study (range, 7-12 years), and all of them had experienced severe symptoms induced by dairy products containing small amounts of heated egg (less than 2 g) within 1 year before the treatment. All subjects had asthma and atopic dermatitis, and 4 (67%) subjects had allergy to at least one other food. The median threshold dose (minimum dose inducing allergic reaction) of egg white confirmed by DBPCFC was 0.152 g (range, 0.012-0.360 g), expressed as real egg white, and the most common induced objective symptom was vomiting (83%), the next being skin urticaria (50%). None of the subjects responded to placebo.

RUSH SOTI

Table 3 summarizes the course of rush SOTI. Eventually, all subjects could tolerate more than 60 g of heated egg at the end of rush SOTI, which took 12 days (range, 9-18 days). Patients stayed at home during weekends and holidays, when they were asked to keep ingestion of the fixed dose of egg white, hence the actual number of days necessary to achieve tolerance to one whole egg was 9 days (7-13 days). Figure 1 shows the daily process of each subject to attain the tolerance to 60 g of egg during rush SOTI. Sixty grams of egg is equivalent to one whole egg of medium size.

All children experienced some side-effects during rush SOTI. These allergic symptoms which included

Table 2 Patient characteristics

Subject no.	Sex	Age	Recent history induced by heated egg (< 2 g) † (age and symptoms)	Threshold dose ‡ at DBPCFC	Symptoms at DBPCFC	Complications	Other food allergies
001	F	9 y 8 m	9 y 2 m AP, VO, DI, SW, OP	0.360 g	AP, VO, UR, SW, OP	Asthma, AD	Peanuts, shellfish
002	M	8 y 5 m	8 y 0 m UR, WH, DY	0.012 g	UR, DY, RH, SN	Asthma, AD, AR	Peanuts
003	M	12 y 0 m	11 y 3 m AP, VO, DI, UR, SW, OP	0.296 g	AP, VO, DI, OP	Asthma, AD, AR	None
004	F	7 y 2 m	6 y 9 m UR, SW, WH, DY	0.200 g	AP, VO, DI, UR	Asthma, AD, AC	Milk
005	M	9 y 4 m	8 y 10 m AP, VO, UR, WH, DY, OP	0.088 g	AP, VO, OP	Asthma, AD	Milk
006	M	11 y 4 m	10 y 10 m AP, VO, DI, UR, OP	0.104 g	AP, VO, OP	Asthma, AD	None
Median		9 y 8 m		0.152 g			

AP, abdominal pain; VO, vomiting (severe and repetitive); DI, diarrhea; UR, urticaria; SW, swelling; WH, wheeze; DY, dyspnea; RH, rhinorrhea; SN, sneezing; OP, oral pruritus; AD, atopic dermatitis; AR, allergic rhinitis; AC, allergic conjunctivitis.

† All of subjects had the allergic reactions after ingestion of dairy products containing less than 2 g of heated egg requiring emergency treatment.

‡ The dose is expressed as real egg white, though DBPCFC was performed with powdered egg white.

Table 3 Outcome of rush SOTI

Subject no.	Threshold dose at DBPCFC	Tolerated dose† at the end of rush SOTI	Time to reach 60 g of egg	Symptoms during rush SOTI
001	0.360 g	≧ 60 g	18 days (13 days)‡	AP, UR, SW, WH, OP
002	0.012 g	≧ 60 g	13 days (9 days)	UR, RH, SN
003	0.296 g	≧ 60 g	9 days (7 days)	AP, OP
004	0.200 g	≧ 60 g	10 days (8 days)	UR, SW, WH, RH, SN
005	0.088 g	≧ 60 g	15 days (11 days)	AP, DI, OP
006	0.104 g	≧ 60 g	11 days (9 days)	AP, DI, OP
Median	0.152 g	≧ 60 g	12 days (9 days)	

AP, abdominal pain; DI, diarrhea; UR, urticaria; SW, swelling; WH, wheeze; RH, rhinorrhea; SN, sneezing; OP, oral pruritus.

† When reaching 1,000 mg of powdered egg white, which is equivalent to 8 g of real raw egg white, the material was changed to 8 g of heated egg (scrambled egg).

‡ Figures in parentheses do not include the days the same dose was ingested at home during refreshment.

wheezing were found regardless of changes to scrambled egg in all patients. Mild symptoms, such as sole urticaria, mild abdominal pain, and oral pruritus, were controlled by oral antihistaminics if needed. No vomiting was observed. Subjects 001 and 004 experienced mild wheezing without dyspnea, once (day 11) and twice (day 4 and day 9) respectively, and they received single inhalation of a bronchodilator, which brought prompt resolution of symptoms without adrenaline treatment. Two subjects (005 and 006) experienced abdominal pain with single diarrhea once a few hours after the dosing, and they were treated with oral antihistaminics without further reactions. Only one subject (004) received additional oral steroid only once because she experienced severe urticaria all over her body. None of the subjects experienced any serious reaction requiring adrenaline, intravenous fluids, or oxygen treatment.

All subjects are now between 16-21 months after rush SOTI keeping ingestion of more than one heated whole egg at least twice a week, and none of them have symptoms.

As for the oral challenge test of 1 g of powdered egg at 9 to 12 months after starting maintenance, 3 of 6 subjects tolerated with no symptom, 2 subjects responded with single vomiting, and the other responded with abdominal pain and single mild diarrhea, which did not apply to the positive allergic reaction criteria in DBPCFC just before rush SOTI.

LABORATORY FINDINGS

Laboratory findings are shown in Figure 2. Egg white-specific IgE levels tended to increase at the end of rush SOTI, and thereafter began to decrease, had tendencies to decrease, and decreased significantly at 12 months from rush SOTI compared with the levels

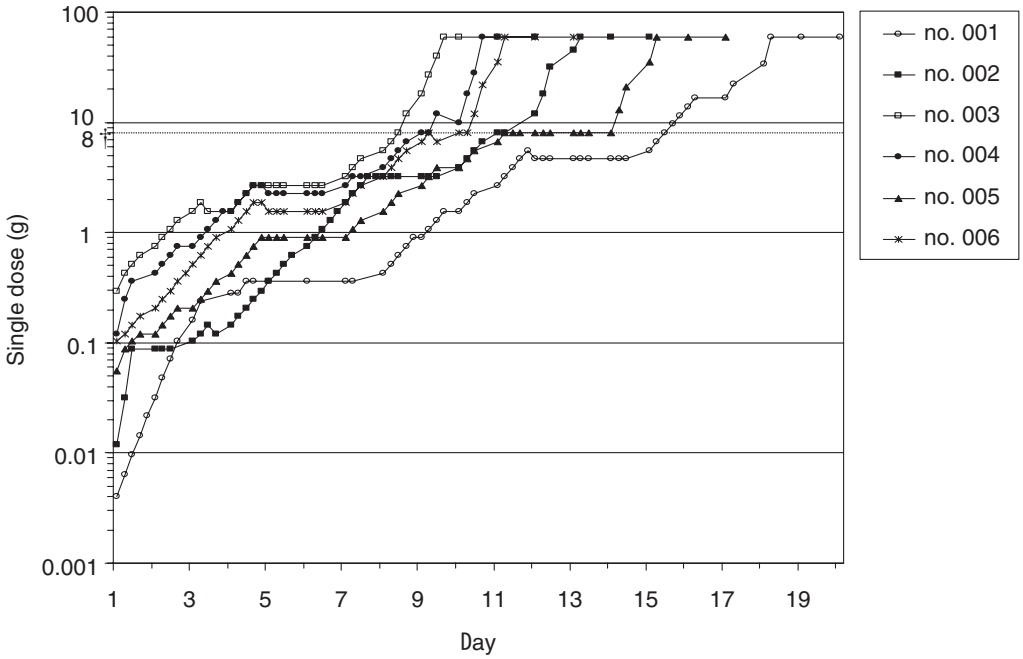

Fig. 1 Daily process to attain the tolerance to 60 g of egg during rush SOTI. The abscissa shows the days after starting rush SOTI. The ordinate shows the single doses plotted in logarithmic scale. The dose is expressed as real egg white. One gram of powdered egg white is equivalent to 8 g of real raw egg white. †When the dose reached 1 g of powdered egg white, we changed the material to scrambled egg starting at 8 g.

before rush SOTI (P = 0.028). Ovomucoid-specific IgE levels significantly decreased at 12 months after rush SOTI, too (P = 0.028). Egg white-specific IgG_4 levels increased significantly at 12 months after rush SOTI (P = 0.043). Histamine release test of egg white decreased in 4 subjects, while they did not decrease in 2 subjects at 12 months after rush SOTI, and the differences compared with the data before rush SOTI were not significant. Th1/Th2 ratio decreased significantly at 6 months after rush SOTI (P = 0.047), but the changes were not significant at 12 months. Serum levels of IL-4 and IFN-γ did not change significantly (data not shown). Serum levels of IL-10 decreased and plasma levels of TGF-β1 increased from 6 months after rush SOTI compared with the levels before rush SOTI, and the changes were significant (P = 0.043 and P = 0.047 respectively). In regard to skin prick test, the changes in skin prick test resulted in no significant decrease (data not shown).

DISCUSSION

In recent years, several studies of SOTI have been reported. Morisset *et al.*[19] reported that oral desensitization helped allergic children to overcome their allergy, while the avoidance of allergic foods was likely to increase sensitization and to lower the threshold of reactivity. But the efficacy rates for complete tolerance obtained in previous studies were between 36% and 83%.[14-20] Moreover, most of the subjects were very young children and previous studies of SOTI took a long time for treatment, at least 3 months to several years, which made it difficult to differentiate actual effects of the treatment from natural outgrowth. Longo *et al.*[18] reported the data of SOTI for 1 year for cow's milk allergy. They carried out the procedure as rush mode for the first 10 days, and the success rate in this phase was only 30%. There are few reports in this area in regard to acquisition of complete tolerance in a very short period in patients of school-age and over, except for some case reports.[29-31]

Our study shows that our rush SOTI can induce tolerance to the causative food in school-age patients with severe food allergy in a few weeks. Although the threshold dose of raw egg white at DBPCFC before treatment was only 0.152 g (median), all subjects tolerated at least 8 g of raw egg white and they could reach one whole heated egg (60 g) through rush SOTI. Though subject number was not enough yet, this success rate was 100%. Our experiences and prior studies in rush immunotherapy for aeroallergens and some successful reports about rapid desensitization in patients with aspirin hypersensitivity were hints for us to make our original rush SOTI protocol.[23,24,32] We assume that the refractory state during repeated exposure to the allergen may reduce the

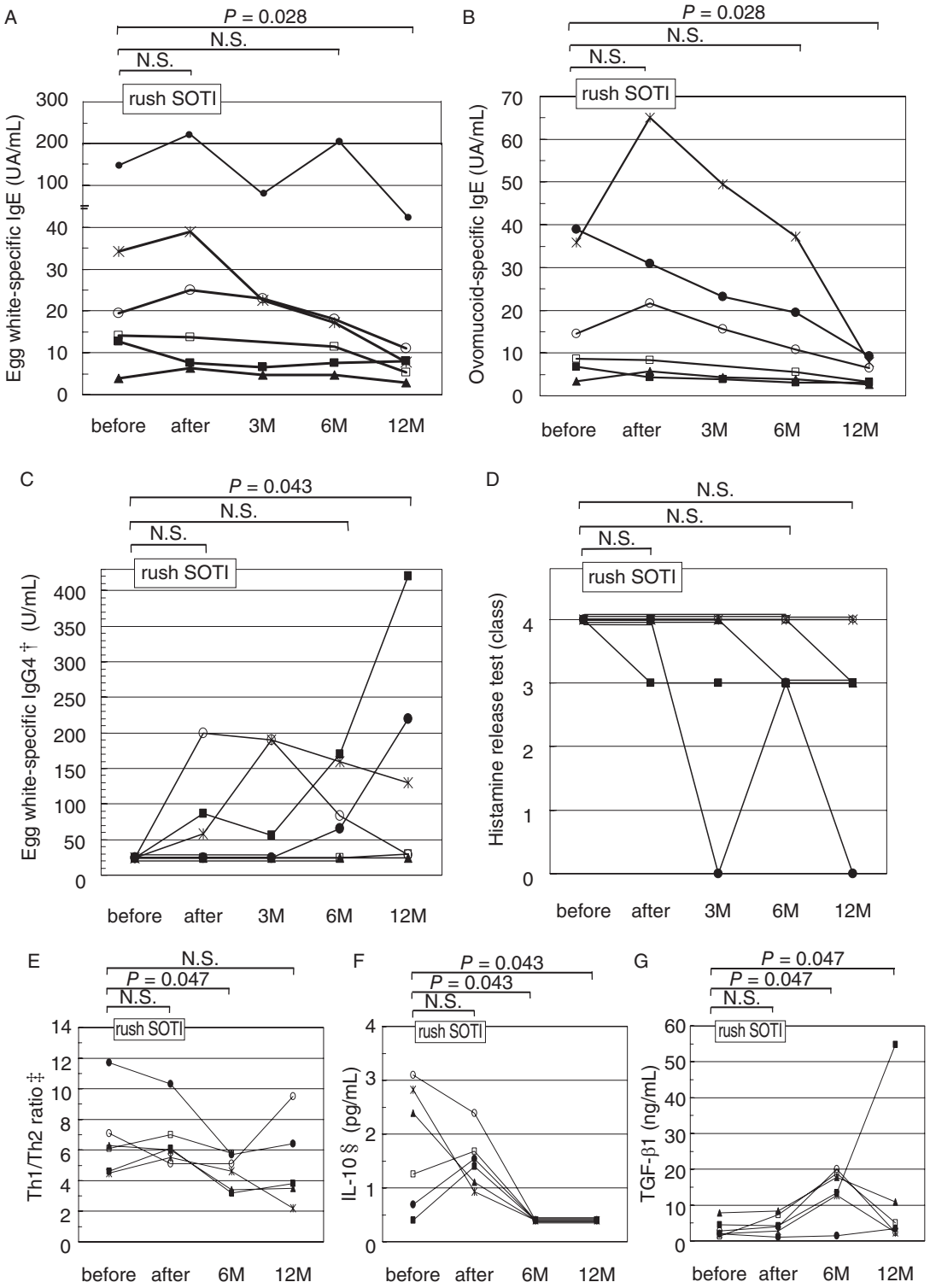

Fig. 2 Laboratory findings. Blood samples were collected just before DBPCFC (before), on the last day of rush SOTI (after) and at 3 months (3M), at 6 months (6M) and at 12 months (12M) after starting maintenance. **A,** egg white-specific serum IgE. **B,** ovomucoid-specific serum IgE. **C,** egg white-specific serum IgG_4. **D,** histamine release test of egg white. **E,** T helper 1/T helper 2 ratio. **F,** serum IL-10. **G,** plasma TGF-β1. † A 24 U/mL value was assigned to <25 U/mL values (the lowest limit of detection of this technique). ‡ T helper 1 (Th1, IFN-γ+/IL-4-/CD4); T helper 2 (Th2, IFN-γ-/IL-4+/CD4). § A 0.4 pg/mL value was assigned to <0.5 pg/mL values (the lowest limit of detection of this technique).

intensity of symptoms induced by the allergen, though the precise mechanisms are not clear. Some papers show immunologic unresponsiveness for a short time after stimulation, which is called desensitization.[33,34]

In the literature on SOTI, side-effects are reported in 50-100% of the cases.[14-20] In our rush SOTI, all children experienced side-effects to some extent. This result might be explained by the fact that all our patients had severe food allergy and they did not receive oral antihistaminics on a regular basis so as not to mask any allergic reaction. The symptoms experienced during rush SOTI period were easily controlled by oral antihistaminics, except rare cases which needed inhalation of beta agonist or oral corticosteroid. No subject required adrenaline, intravenous fluids, or oxygen treatment. Furthermore, in our rush SOTI, doses of food were increased only in the hospital, so patients had no need to bother about allergic reactions at home while many other studies of SOTI caused reactions at home. Compared with previous SOTI in children with severe food allergy,[18] our rush SOTI seems to be safer, quicker and more effective.

Many previous studies of SOTI in humans showed that egg-specific serum IgE levels decreased once oral tolerance was acquired[14-20] and egg-specific serum IgG_4 levels increased[15,20]; this was not the case in our study of rush SOTI. We found no statistical changes in egg white-specific serum IgE levels and ovomucoid-specific serum IgE levels at the end of rush SOTI. Those changes appeared significantly after one year from rush SOTI. This strongly suggests the mechanisms by which tolerance was acquired, being independent of a decrease in specific IgE to the allergen, during rush SOTI. Egg white-specific serum IgG_4 also increased significantly after more than 6 months. Only a few previous studies refer to skin prick test, and they reported a decrease of the wheals after a 6-month or more period of SOTI.[15,16,19] We found no significant decrease in skin prick test by one year.

Though the mechanisms of SOTI in humans are not clear yet, the mechanisms of oral tolerance in mice were analyzed. Chehade and Mayer[35] referred to the relation between oral tolerance and the mucosal immunologic organ. Oral tolerance can be induced after administration of either a single high dose of antigen or repeated lower doses. A high-dose of an oral antigen can induce lymphocyte anergy or deletion. Low-dose tolerance is mediated by regulatory T cells, such as T_H3 cells, T_R1 cells, $CD4^+$ $CD25^+$ cells, $CD8^+$ cells and natural killer T cells, and by cytokines, such as IL-10 and TGF-β. In our study, IL-10 decreased and TGF-β1 increased from 6 months after rush SOTI. The role of TGF-β in the induction and/or maintenance of oral tolerance have been much debated, with many reports suggesting an important role for TGF-β.[36,37] Previous reports on IL-10 showed various data. Recent animal models of food allergy demonstrated the important roles of IL-10 in oral tolerance.[38,39] And Alonso *et al.* reported that increased serum IL-10 level is a useful tool in the diagnosis of food tolerance in previously food-allergic patients.[40] Contrary to these papers, in our rush SOTI, IL-10 did not seem to be an important factor for oral tolerance. Some different mechanisms would induce oral tolerance. Some papers in which IL-10 did not appear to be directly involved in the effecter or maintenance phase of tolerance in animal models of oral tolerance support these findings.[36,41] Th1/Th2 ratio decreased significantly only at 6 months after rush SOTI in our study in humans. Some papers reported both Th1 and Th2 responses were suppressed in animal models,[36,41] but mechanisms of the phenomena were not clear. Also the reason why histamine release caused by egg white in blood of the subjects did not decrease when the subjects could ingest the food without symptoms is unknown.

Although our trial was an uncontrolled study, the effect of this rush SOTI would be evident because we identified symptoms by egg allergy by DBPCFC just before the treatment, and it would be unlikely that the allergic condition would vanish naturally in a few weeks, especially at the ages of our subjects. All subjects had had severe allergic reactions after ingestion of less than 2 g of heated egg within 1 year before this treatment, and in fact all of them had allergic symptoms that included wheezing by ingestion of scrambled egg during rush SOTI. However, at last all of them could attain tolerance to more than one whole egg. Further investigations are necessary to analyze the precise mechanisms involved in the rapid acquisition of tolerance to food and to improve the practical procedures of this rush SOTI to be safer and more effective. We will continue to follow and investigate this phenomenon of our rush SOTI, and try to increase subjects for this trial using egg and other kinds of food.

In conclusion, we have shown that our rush SOTI is a very effective and safe treatment for food allergy, which induces oral tolerance during only 12 days in school-age children with severe food allergy without experiencing severe side effects. Although further studies involving a large group of patients and thorough analyses of the mechanisms are needed, we consider that this method is a promising maneuver that would replace allergen avoidance as the therapy for food allergy.

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