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Key for Successful Home-Based Slow Oral Immunotherapy in Children with Egg Allergy: Age and Sensitivity

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Abstract

Background: Oral immunotherapy (OIT) has been recognized as a promising therapy for children with food allergy. However a part of applied patients was not able to increase doses of allergic food. Since a clear standard for the appropriate patient selection for OIT has not been established, we tried to determine the indication criteria for when and/or to whom OIT should be applied.

Method: We retrospectively reviewed the medical records of 82 children treated by home-based slow OIT which shows the administration of baked eggs orally every 2-3 days at home for two months as maintenance dose after open food challenge and statistically analyzed their clinical courses to identify the prognostic factors associated with a successful result. We applied the variables such as age, sex, symptoms during OIT, initial dose when starting OIT, specific IgE level and dislike of eggs, to a multivariate stepwise logistic regression analysis.

Results: A total of 40 (56%) children reached remission in the OIT trial for a median of 213 days without severer allergic reactions, the remaining 31 (44%) could not reach the remission stage. We found the clinical course of the patients to be significantly associated with age and the initial dose of OIT. The children under 4 years of age or who could ingest larger portions (more than 1g if under 4 years, and 6g if over 5 years) as an initial dose were found to be the best candidates for OIT.

Conclusions: This study revealed that home-based slow OIT caused almost successful results without severe allergic results in the children with egg allergy, and especially when starting before 5 years of age it is remarkable even if their initial doses were limited. This is the first report to contribute to the establishment of the indication criteria for home-based OIT.

Keywords: Egg allergy; Indication criteria; Prognostic factor; Oral immunotherapy

Introduction

Egg allergy is one of the most frequent food allergies in Japan affecting about 1 to 5% of young children [1]. Common symptoms of egg allergy involve the skin as well as the digestive tract, and in more severe cases, can also result in anaphylaxis. Although two- thirds or more of these children outgrow the allergy by around 6 years of age [1-3], one- third of the population of children continues to suffer from persistent allergic reactions. Oral immunotherapy (OIT) is a promising therapy for food allergies, especially for IgE-mediated cow's milk and hen's egg allergies, during childhood [1,4-12].

Most of OIT regimens include weekly dose increases in the hospital setting, with dose maintenance during the week, taking from 12 to 24 weeks (or even more) to reach the final dose. Recently, schedules with a duration of only a few days have been introduced but they require that the treated patient be admitted to the hospital or at least attend the hospital daily because of frequent severe adverse reactions.

We designed new protocol for more safety and avoiding inconvenience of both children and their parents in the children with egg allergy. The new protocol is more slowly increased dose than conventional OIT regimens and the children ingest only 3 days per week.

In the past two years, we have applied the new protocol of OIT (so called home-based slow OIT) to young children with egg allergy. In our experiences, a certain population of children still showed a persistence of their egg allergy, although the majority of children obtained favorable results (unpublished data). As Kurihara has reviewed, it might be important to clarify the indication criteria with regard to which type of patients each therapy should be applied [1]. In the present study, we have statistically analyzed the outcomes of home-based OIT for children with egg allergy to elucidate the prognostic factors for this therapy.

Patients and Methods

Home-based slow OIT was conducted on 82 children (53 males and 29 females) at a median age of 5 years (interquartile range (IQR), 3 years) who had been diagnosed with egg allergy by a food challenge test at Kansai Medical University, Osaka, Japan. The survey was retrospectively carried out based on the medical records of these children. We statistically analyzed the clinical course of the therapy to elucidate the prognostic factors for a successful result.

Oral food challenge test

All egg-food challenges were open challenges, performed in

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hospital settings and supervised by physicians in accordance with the guidelines for diagnosis and management of pediatric food allergy in Japan [13]. During the challenge, full emergency equipment was at hand. The children's parents prior to enrolment in the study gave informed consent. Patients taking anti-histamines were asked to avoid them at least 48 h before provocation but topical steroids were authorized, and were admitted to our day-clinic in the morning in a fasting state. Challenge material was cooked egg baked for 3 min and then steamed for 10 min for open challenges. The initial challenge dose and the following doses were set according to the history of the last reaction, but were similar in most patients. If the patient tolerated the first dose, subsequent doses were given every 30 min. Doses and time intervals between them were adjusted in accordance with symptoms observed during the challenges. The challenge was interrupted if children demonstrated unambiguous clinical reactivity or after the administration of 45 g of egg. All children were then observed for at least three more hours after the end of the feeding.

Home-based slow OIT

All the subjects were outpatients. We used baked egg as previously described. The initial dose of home based slow OIT was set to be a sub threshold dose, usually one fourth or one eighth of the threshold dose determined during a preliminary open challenge test. The initial dose, if no adverse reactions existed, was administered orally every 2-3 days at home for two months as a maintenance dose. The children were challenged to ingest a double dose under medical supervision at every two-month follow-up visit. They repeated the escalation phase in the same manner until being able to ingest a half of an egg, which was defined as a remission dose. They were encouraged to continue ingesting a further increased dose in a less cooked condition even after reaching the remission dose.

Laboratory test

Blood samples were collected before starting OIT, during the remission stage or after 6 months if remission was not reached, and 12 months after starting OIT. They were analyzed for egg white-specific serum IgE quantified using the Phadia CAP System FEIA (Phadia, Uppsala, Sweden).

Patient selection for analysis

There were 7 children who could not start OIT because of mild to severe allergic reactions to the initial dose on the first day of OIT trial. Four children did not appear either on the first day of the trial or during the subsequent planned visits. We excluded the 11 above-mentioned children from the study population, and statistically analyzed the remaining 71.

Statistical analysis

The clinical records of the children were overviewed and classified into two groups according to the outcome of OIT: one group consisted of responders who could reach remission and continued to show progress throughout the following period; another group consisted of poor responders who showed persistent allergic reactions and could not reach the remission stage, or who showed regression and lost desensitization during the maintenance phase after reaching the remission stage. In order to identify what caused the differences between the two groups, we analyzed the outcome of the therapy to see if any of the following factors were significantly different between the above two groups; sex, age at starting OIT, egg-specific IgE level before starting OIT, the initial dose used for OIT, symptoms during the clinical course (digestive, skin, respiratory, otorhinologic), and dislike of eggs. For statistical analysis of the receiver operating characteristics (ROC) of age at starting OIT plots between the two groups, the optimal cut-off values showed 4.5 years of age and therefore we divided the age criteria into two groups; younger and older; that is, over 5 and under 4. The egg-specific IgE values of class 6(>100 UA/ml) were assigned a value of 101 UA/ml and class 0(<0.35 UA/ml) was assigned a value of 0.15 UA/ml. The initial dose of OIT was indicated at 1/2, 1/4, 1/8, 1/16 or even smaller partitions (power of 2) of an egg, where a middle-sized raw egg weight were considered to be 64 g. The data with a skewed distribution were analyzed after a logarithmic transformation. We used the SPSS (version 11.0 for Windows) software package, with a multivariate stepwise logistic regression analysis with a forward selection method. The factors included were gender (1 for male, 0 for female), age (1 for ≥ 5, 0 for ≤ 4), Log2 (egg-specific serum IgE), and Log2 (initial dose), digestive symptoms (1 or 0), skin symptoms (1 or 0), otorhinologic symptoms (1 or 0), respiratory symptoms (1 or 0) and dislike of eggs (1 or 0). p values of <0.05 (by two-tailed tests) were considered to be significant.

Results

The median age of the 71 children at the initial challenge of OIT was 5 years (IQR, 3 years). There were 27 children under 4 years of age (38%) and 44 over 5 years of age (62%). There were 48 male (68%) and 23 female (32%) children. When the children become tolerant and could ingest half of an egg, we define this phase as remission. The phase before reaching remission is described as tolerance for the processed material. A total of 40 (56%) children reached remission in the OIT trial and continued to be encouraged to ingest further increased doses. The remaining 31 (44%) could not reach the remission stage, but were also encouraged to continue ingesting the highest tolerated doses, and were challenged to increase them at regular visits. There was no child who experienced a severe adverse reaction throughout the course. Only antihistamine drugs and corticosteroid ointment were used to treat the symptoms but epinephrine was never used as a rescue-treatment. In all, the children took a median of 213 days (IQR, 225 days) to reach remission. We have followed them up for a median of 340 days (IQR, 323 days) since the initial challenge.

The children were classified into two groups according to their clinical patterns, as shown in Figure 1. One consisted of OIT responders who reached the remission and have continued to ingest further increased doses, while the others consisted of poor responders who could not either reach the remission stage or who showed regression

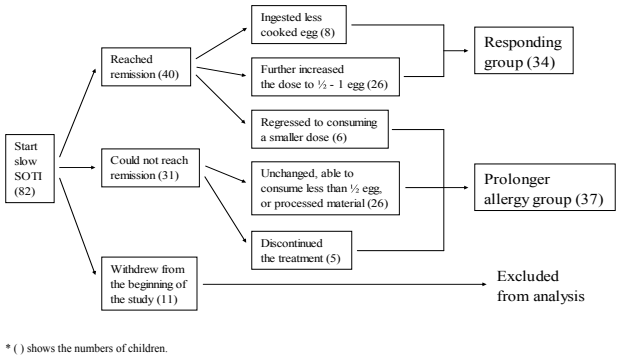


Figure 1: Classification according to the clinical patterns of children treated with home-based slow OIT.

		Responding	Prolonged	Total
Age	≤ 4 yrs	19 (70.4%)	8 (29.6%)	27 (100%)
	≥ 5 yrs	15 (34.1%)	29 (65.9%)	44 (100%)
Sex	female	12 (52.2%)	11 (47.8%)	23 (100%)
	male	22 (45.8%)	26 (54.2%)	48 (100%)
Digestive symptoms	no	23 (54.8%)	19 (45.2%)	42 (100%)
	yes	11 (37.9%)	18 (62.1%)	29 (100%)
Skin symptoms	no	11 (39.3%)	17 (60.7%)	28 (100%)
	yes	23 (53.5%)	20 (46.5%)	43 (100%)
Otorhinologic symptoms	no	27 (43.5%)	35 (56.5%)	62 (100%)
	yes	7 (77.8%)	2 (22.2%)	9 (100%)
Respiratory symptoms	no	24 (50.0%)	24 (50.0%)	48 (100%)
	yes	10 (43.5%)	13 (56.5%)	23 (100%)
Dislike of eggs	no	30 (48.4%)	32 (51.6%)	62 (100%)
	yes	4 (44.4%)	5 (55.6%)	9 (100%)
Total		34 (47.9%)	37 (52.1%)	71 (100%)

Table 1: Crosstabulation for the Clinical Course.

	Beta	SE	*p* value	OR	95% CI for OR
Age	1.448	0.582	0.013	4.255	1.360-13.318
Dose	-0.588	0.188	0.002	0.556	0.384-0.804
Constant	-3.440	0.993	0.001	0.032	

*The factors included were gender, age, egg-specific IgE, initial dose, symptoms during the clinical course
(digestive, skin, respiratory, otorhinologic) and dislike of eggs. Only significant results are shown
*Beta: regression coefficient in the equation
*SE: Standard Error of Beta
*OR: Odds Ratio (prolonged/responding)
*CI: Confidencelinterval

Table 2: Variables Included in the Regression Equation.

after reaching remission, thus resulting in a prolonged sensitivity to eggs. A total of 34 (48%) children belonged to the responding group, and 37 (52%) to the prolonged sensitivity group. The median age was 4 years (IQR, 3 years) in the responding group, and 5 years (IQR, 2 years) in the prolonged group. Table 1 (1 to 7) shows the number of cases of each factor (age, sex, digestive, skin, otorhinologic, respiratory symptoms and dislike of eggs) analyzed in the two groups. With regard to the specific IgE level, the median egg-specific IgE was 7.6 UA/ml (IQR, 13.6 UA/ml) in the responding group and 15.0 UA/ml (IQR, 22.5 UA/ml) in the prolonged group. The median initial dose on OIT was 4.0g (IQR, 6.0g) in the responding group and 1.0 g (IQR, 3.0 g) in the prolonged group, as shown in Figure 2.

We applied the above-mentioned variables to a multivariate stepwise logistic regression analysis and found that the clinical course of the patients was significantly associated with their age and initial dose of OIT (Table 2). The regression equation obtained by Table 2 was determined as below, where *p* stands for the probability of belonging to the responding group:

$$\mathrm{logit}(P) = \log_e \frac{P}{1-P} = \begin{cases} -3.440 - 0.588 \log_2 (\mathit{intial\ dose}) & \text{if } \mathit{age} \le 4 \\ -3.440 + 1.448 - 0.588 \log_2 (\mathit{intial\ dose}) & \text{if } \mathit{age} \ge 5 \end{cases}$$

We described the probability curve based on the regression equation above as shown in Fig.3, showing the relationship between an initial dose and the probability of a child belonging to the responding group. Clear differences were found in the two groups. Briefly, if a child over 5 years could ingest about 1g as an initial dose, the probability of his/her belonging to the responding group was about 22%, while the same probability was 55% if he/she was under 4 years of age (Figure 3).

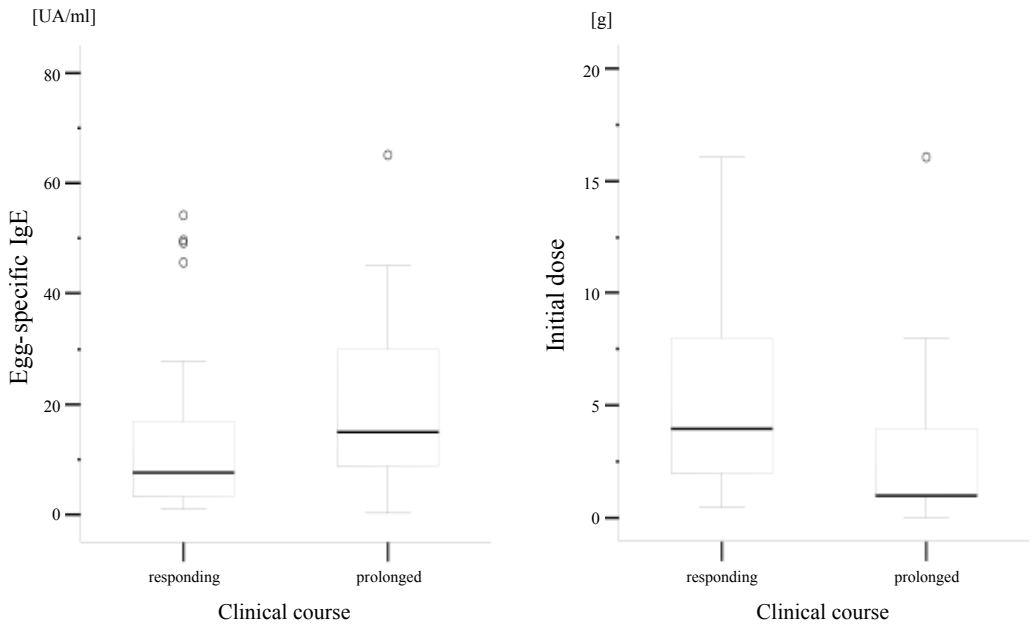
Discussion

In the present study, home-based slow OIT was shown to be more successful for the children with egg allergy less than 4 years of age if they were able to ingest over 1 g in weight of raw egg as an initial dose. However, we can see that children over 5 years of age must ingest much more egg as an initial dose to obtain successful results using the same method. In order to reach a 50% success level, we were able to determine how much egg the children are required to ingest as an initial dose by substituting the value p/1-p=1 in the above equation, which gives the initial dose required to reach the 50% borderline as follows: $(\mathit{initial\ dose})_{p=0.5}$=1.11 g if age ≤ 4, 6.11 g if age ≥ 5.

This means that a child over 5 years of age needs to ingest more than 6 g as an initial dose to reach 50% success. This dose could be one of the indication criteria to judge whether a child over 5 years of age should be put on home-based OIT or whether other immunotherapies, such as rush OIT, should be used [1,4,6,8,10-12,14,15]. However, even if the child is over 5 years of age, as long as severe sensitivity is not present, the child may still have a good chance of overcoming the allergy by home-based OIT. Needless to say, a child under 4 years has a larger possibility of success, even if he/she could only ingest a small amount of egg as an initial dose, as he is only required to ingest about 1g as an initial dose to reach the 50% borderline for success.

Younger children are generally believed to outgrow food allergies by age 3, although the outgrow rate varies according to different studies [2,16-20]. Several studies have pointed out that the outgrow rate was lower than previously reported, and that there were certain populations of children who could not outgrow an allergy on their own [3,17,20]. A high antigen- specific IgE level was reported to be one of the predictive factors for egg allergy persistence [3,18,21]. Therefore, it was of interest to elucidate whether slow OIT could alter the natural course of children who have difficulty outgrowing an egg allergy. Ramesh et al. described that it is not very clear whether total avoidance of the specific food increases the chances of outgrowing the allergy, or if the introduction of small amounts increases tolerance [2]. Staden et al. performed a control study to assess the effects of OIT. They commented that OIT substantially increases the threshold dose necessary to elicit allergic reactions, and children who undergo OIT could reach their maintenance dose much faster than the children on an elimination diet. In this respect, OIT is considered to be superior to an elimination diet [12]. Indeed, some control studies have been reported on OIT (rush manner) for older children with a milk allergy, and they found no improvement in an elimination group [8,22]. Thus, several studies have indicated that OIT may alter the natural course or increase the threshold dose in children who have difficulty outgrowing their food allergy.

Our study unfortunately lacked a control group, and it is therefore not possible to demonstrate the superiority of home-based OIT to an elimination diet. However, we suggest that leaving children with persistent egg allergy up to 5 years of age without medical intervention may deprive them of chances of overcoming egg allergy by home-based OIT, which seems to be a safer and more practical approach than rush OIT because it does not require hospital admission. Compared with rush OIT, where most of the applicants have experienced adverse reactions [8,10], our home-based slow OIT caused almost no side-effects, except for occasional very mild to moderate symptoms, which did not require adrenaline, intravenous fluids, or oxygen treatment. While many other OIT approaches, including rush OIT, caused reactions at home, the patients under our slow OIT protocol were not bothered by allergic symptoms at home, because the doses of egg were only increased in the outpatient clinic. It is also necessary to point out that the safety of



* Horizontal lines, boxes, whiskers, and circles represent median values, interquartile ranges, minimum or maximum values, and outliers, respectively.

Figure 2: Level of specific egg-white IgE (left) and the initial dose used for home-based slow OIT (right) between the responding group and prolonged allergy group.

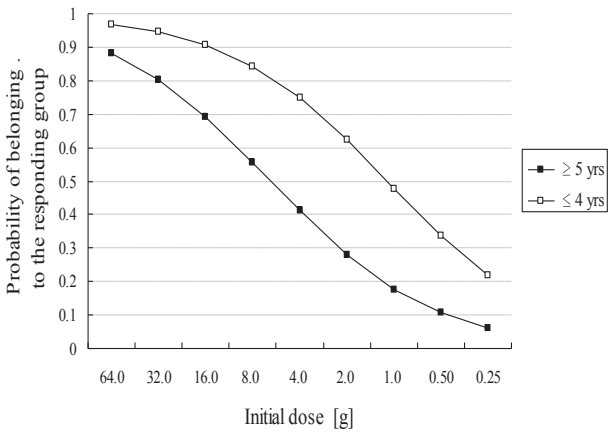


Figure 3: Probability curve for belonging to the responding group.
The relationship between the initial dose and the probability of a child belonging to the responding group between the two groups (over 5 or under 4 years) is shown.

the method makes it possible to treat more patients at the dispensary, while only a few rush OIT patients can be treated because of the need for hospitalization.

In conclusion, home-based slow OIT leads to successful result without any severe allergic reactions when starting OIT before 5 years of age may be critical, because at that time, the children would have a greater possibility of overcoming their egg allergy by home-based OIT, and before they become less likely to be responsive.

Contributions of the Authors

Conception and design (Kyoko Sudo, Shoichiro Taniuchi), acquisition of data (Kyoko Sudo, Shoichiro Taniuchi, Shindo Okamoto, Yasuko Hatano, Keiji Nakano, Tomohiko Shimo), analysis and interpretation of data (Kyoko Sudo[1], Shoichiro Taniuchi, Shindo Okamoto, HK), drafting of the manuscript (Kyoko Sudo, Hayato Koshino), critical revision (Kyoko Sudo, Shoichiro Taniuchi, Shindo Okamoto, Hayato Koshino), statistical analysis (Hayato Koshino), and supervision (Shoichiro Taniuchi, Kazunari Kaneko) was done by the respective authors.

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