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Original article

Desensitization to a whole egg by rush oral immunotherapy improves the quality of life of guardians: A multicenter, randomized, parallel-group, delayed-start design study

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CRTH2, chemoattractant receptor-homologous molecule expressed on TH2 lymphocytes; DBPCFC, double-blind, placebo-controlled food challenge; EWP, egg white powder; FAQL-PB, the Food Allergy Quality of Life – Parental Burden Questionnaire; OIT, oral immunotherapy; QOL, quality of life; RCT, randomized controlled trial; rOIT, rush oral immunotherapy; TD, threshold dose

ABSTRACT

Background: Patients with food allergies and their families have a significantly reduced health-related quality of life (QOL).

Methods: We performed a multicenter, randomized, parallel-group, delayed-start design study to clarify the efficacy and safety of rush oral immunotherapy (rOIT) and its impact on the participants' daily life and their guardians (UMIN000003943).

Forty-five participants were randomly divided into an early-start group and a late-start group. The early-start group received rOIT for 3 months, while the late-start group continued the egg elimination diet (control). In the next stage, both groups received OIT until all participants had finished 12 months of maintenance OIT.

Results: The ratio of the participants in whom an increase of the TD was achieved in the first stage was significantly higher in the early-start group (87.0%), than in the late-start group (22.7%). The QOL of the guardians in the early-start group significantly improved after the first stage (65.2%), in comparison to the late-start group (31.8%). During 12 months of rOIT, the serum ovomucoid-specific IgE levels, the percentage of CD203c⁺ basophils upon stimulation with egg white, and the wheal size to egg white were decreased, while the serum ovomucoid-specific IgG4 levels were increased. However, approximately 80% of the participants in the early-start group showed an allergic reaction during the first stage of the study, whereas none of the patients in the late-start group experienced an allergic reaction.

Conclusions: rOIT induced desensitization to egg and thus improved the QOL of guardians; however, the participants experienced frequent allergic reactions due to the treatment.

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Introduction

Egg allergy is one of the most common food allergies in Japan, where it affects approximately 1–5% of young children.¹ It may cause severe allergic reactions in sensitized children.² Although two thirds of children with egg allergy will outgrow their condition by 6 years of age, most school-age patients who have not developed tolerance by that age have egg allergy for a long period of time.^{3,4}

Due to dietary limitations imposed by strict allergen avoidance, it has been shown that patients with food allergies and their

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families have a significantly reduced health-related quality of life.^{5,6} In recent years, trials have been carried out to investigate the effectiveness of oral immunotherapy (OIT) for food allergy.⁷ However, a few studies, which involved peanut allergy, focused on the QOL of the guardians.^{8,9} Thus, we performed a randomized controlled trial (RCT) of rush OIT (rOIT) for severe egg allergy to clarify the efficacy and safety of rOIT as well as the impact on the daily life of the participants and their guardians.

Methods

Trial design

We performed the present multicenter, randomized, parallel-group, delayed-start design study to clarify the efficacy and safety of rOIT for hen's egg allergy, and the impact on the daily life of the participants and their guardians (UMIN000003943). The study was performed according to The Declaration of Helsinki Principles. The study protocol was approved by the Ethical Review Board of Mie National Hospital (Approval number, 22-7). Written informed consent was obtained from each of the study participants and their guardians. The protocol was divided into 2 stages. In the first stage, the participants were randomized into an early-start group or a late-start group to assess the efficacy and the safety of rOIT for hen's egg allergy in comparison to an egg elimination diet at 3 months after the randomization. In the second stage, both groups received OIT to allow more patients to receive active treatment, and to clarify whether the participants achieved a sustained unresponsiveness to egg after 12 months of maintenance OIT. There was no change in the methods after the start of the trial.

Participants

The study took place at 9 allergy centers (university hospitals, national medical centers, and a prefectural medical center) located in urban areas all over Japan. The eligible participants were children of 5–15 years of age with a known history of IgE-mediated hen's egg allergy, with an egg white-specific IgE level of ≥ 0.35 U_A/mL, and positive results in a double-blind, placebo-controlled food challenge (DBPCFC) with ≤ 500 mg of dried raw hen's egg white powder (EWP). The DBPCFC protocol was shown in the outcome section below. The exclusion criteria were uncontrolled asthma, uncontrolled atopic dermatitis or grade 5 anaphylaxis at the time of the DBPCFC.

Interventions

In the first stage, the early-start group received rOIT according to the protocol described below, whereas the late-start group continued the egg elimination diet (control), which had been implemented since before they joined the study (Supplementary Fig. 1). In the second stage, the early-start group continued to receive rOIT, which had already proceeded to the maintenance phase in all of the group's participants, whereas the late-start group started rOIT.

The rOIT protocol consisted of two phases: a rush build-up phase to achieve the ingestion of one medium-sized lightly cooked egg (60 g) and 1 g of EWP in hospital, and a maintenance phase during which the participants continued to take a maintenance dose of egg (60 g of cooked egg and 1 g of EWP) at home. In the rush build-up phase, the initial dose of EWP for each patient was set at 1/10 of the threshold dose (TD), which was determined at the time of the DBPCFC to check the eligibility of each participant. The subsequent doses were increased by approximately 1.2–1.5 times every time and were administered at 30-min intervals, 3–5

times in one day. We monitored and graded their allergic reactions as shown in Supplementary Table 1. If mild allergic symptoms occurred, the participant would continue taking the scheduled dose. If moderate allergic symptoms occurred, the subsequent therapy (on the day) and the first dose of the next day would be the highest dose that the participant tolerated on the day. If severe allergic symptoms occurred, the participant was withdrawn from the study. When the dose reached 1 g of EWP, which was supposed to be equivalent to 8 g of raw egg white, we changed the additional material to scrambled egg heated at 75–80 °C for 10 s. The goal at the rush build-up phase was to consume one whole scrambled egg (about 60 g) and 1 g of EWP. In the maintenance phase, the participants ingested the maintenance dose every day for 2 months, more frequently than every other day over the next 4 months, and more than once every 3 days thereafter at home. In the days on which the participants did not ingest the maintenance dose, they were allowed to consume egg dishes that they liked at home or school to maintain the participants' motivation. Due to the consumption of egg dishes on the days on which the participants did not receive rOIT, the whole amounts of ingested egg were not fixed. However, this did not have an impact on the analyses of the RCT outcomes at the end of the first stage or the analyses of changes during rOIT in the whole study population.

Outcomes

The primary outcome was the increase in the TD of EWP on a DBPCFC during the first stage in the early-start group in comparison to the late-start group (control). Additional analyses were performed to compare the results of skin prick tests, the serum-specific IgE/IgG4 levels to ovomucoid and a basophil activation test using egg white, and the quality of life of the guardians of the patients in the 2 groups. The participants in the early-start group had taken a maintenance dose for about 2 months at home at the end of the first stage, and they performed their usual daily life activities, including going to school and playing sports. Thus, the conditions of the early-start group at the end of the first stage were considered to be similar to the conditions of the late-start group. Further analyses were also performed using the data of all participants who received rOIT both in the early-start group and in the late-start group because the duration of the elimination diet before the initiation of OIT did not differ between the groups. These included the increase in the TD of the EWP by DBPCFC, the changes in the results of skin prick tests, the serum-specific IgE/IgG4 levels to ovomucoid and a basophil activation test using egg white, and the quality of life of the guardians before rOIT treatment, after 3 months of rOIT, and after 2-weeks of egg elimination followed by 12 months of maintenance rOIT. The adverse effects during rOIT were also monitored. The trial outcomes did not change after the trial commenced.

DBPCFC

The DBPCFC was carried out by administering raw hen's EWP K type (Kewpie Corporation, Tokyo, Japan) or placebo (sugar and cornstarch) every 20 min, beginning with an initial dose of 10 mg of powder (equivalent to 80 mg of raw egg white) to 1000 mg of the powder (equivalent to 8000 mg of raw egg white). The dose that caused objective symptoms was considered to be the TD. All of the recruited participants took the DBPCFC to assess their eligibility. The enrolled participants took the DBPCFC for the assessments at the end of the first and second stages.

The skin prick test and serum IgG4 and IgE levels

Egg white extract (Torii Pharmaceutical Co., Ltd., Tokyo, Japan) was used for the skin prick test at each center. The serum-specific

IgG4 and IgE levels were measured using the Phadia CAP System FEIA (Phadia, Uppsala, Sweden).

The basophil activation test

EDTA-containing whole blood was collected from the participants at the above-mentioned time points. The blood samples were transported to Mie national hospital, and the basophil activation test was performed using a commercial kit (Allergen Kit; Beckman Coulter, Brea, CA), according to the manufacturer's instructions. The blood samples were incubated with freeze-dried egg white or ovomucoid purified according to a modification of a previously described method,¹⁰ which was provided by Kewpie Corporation, at 0.1 mg/ml or 1.0 mg/ml for 15 min after the addition of a sufficient amount of calcium solution to neutralize the chelating capacity of EDTA. Basophils were detected on the basis of the forward side scatter characteristics and negative CD3 and positive CRTH2 results. The upregulation of CD203c on basophils was determined using a threshold that was defined by the fluorescence of unstimulated cells (negative control) and which was expressed as the CD203c⁺ percentage.

The quality of life of the guardians

The quality of life of the guardians was evaluated by the Food Allergy Quality of Life – Parental Burden Questionnaire (FAQL-PB)⁵ at the above-mentioned time points. The total score was compared between the groups and between the time points.

Adverse effects

All adverse effects, including allergic reactions to the ingestion of egg, were monitored. Allergic reactions were classified according to the [Supplementary Table 1](#), according to a modification of the Sampson's grading system.² We downgraded "rhinorrhea" and the "sensation of throat pruritus or tightness, cough" because our previous experience showed that these symptoms often occurred but did not interfere with rOIT.

Sample size

Based on the experience results of a previous study,¹¹ we estimated that the TD of EWP might be decreased in >80% of participants. As ratio of the study population that would be expected to outgrow the allergy within 3 months was assumed to be <5%,¹² a sample size of 20 participants per group was necessary to provide 90% power in the detection of a 0.1% difference between the early-start group and the late-start group.

Randomization

The participants were randomized to the early-start group or the late-start group by computer-based 1:1 allocation and were stratified by age, gender, specific IgE levels to egg white, TD of EWP, and the grade of allergic symptoms at DBPCFC. The randomization was performed by an independent data center (Non-Profit Organization Japan Clinical Research Support Unit [J-CRSU], Tokyo, Japan).

Statistical methods

The Mann–Whitney test and the contingency chi-squared test were used to analyze the differences in the baseline data of the early-start and late-start groups. Fisher's exact probability test was used to compare the primary and secondary outcomes and harmful events in the early-start and late-start groups. The relative risk and confidence intervals were also calculated. In cases in which a value of zero caused problems with the calculation of the relative risk, 0.5

was added to all of the cells and the adjusted relative risk was calculated. The Friedman rank test and *post-hoc* Dunn's multiple comparisons test were performed to evaluate the changes in the QOL and the immunological parameters during rOIT. In all analyses, *p* values of <0.05 were considered to indicate statistical significance. The statistical analyses were performed with using the JMP® Pro 12 (SAS Institute, NC, USA) and Prism 6.0 (GraphPad Software, CA, USA) software programs.

Results

The participant flow is illustrated in [Figure 1](#).

Recruitment

We recruited 48 self-selected patients through advertisements in that were displayed in the participating hospitals from July 2010 to March 2011. We checked the eligibility of the participants, including their DBPCFC results. Among them, 2 participants were excluded from the study due to a negative result in response to ≤500 mg of dried EWP on the DBPCFC. One participant was excluded due to grade 5 anaphylaxis at the first DBPCFC. No patients were withdrawn from the study early.

Baseline data

The baseline demographics and clinical characteristics of the early-start and late-start groups did not differ to a statistically significant extent ([Table 1](#)).

The patient numbers

The study outcome that was analyzed was intention-to-treat. All of the participants who were randomly assigned using baseline observation carried forward (the early-start group, *n* = 23; the late-start group, *n* = 22) were included in the analysis. To evaluate the clinical and immunological features after 12 months of rOIT, we analyzed the whole study population including both the early-start (*n* = 20) and late-start (*n* = 18) groups.

Outcomes and estimation

Outcomes during the 1st stage

The ratio of the participants in whom an increase of the TD of EWP was achieved in the first stage was significantly higher in the early-start group than in the late-start group ([Table 2](#)). In addition, 87% of the participants in the early-start successfully achieved a TD of ≥1000 mg, while none of the late-start group members achieved a TD of ≥1000 mg, suggesting that rOIT clearly induced desensitization to egg.

Although the QOL of the guardians was improved in approximately half of the late-start group members (participation bias), the QOL of the guardians in the early-start group showed a significant improvement of ≥10 points in comparison to the late-start group, suggesting that rOIT improved the QOL of the guardians.

We also compared changes in the immunological parameters in the first stage between the early-start and late-start groups. While the serum IgG4 to ovomucoid levels were significantly decreased and the wheal size to egg white was decreased by ≥5 mm in the early-start group; the other immunological parameters did not show statistically significant differences in the first stage.

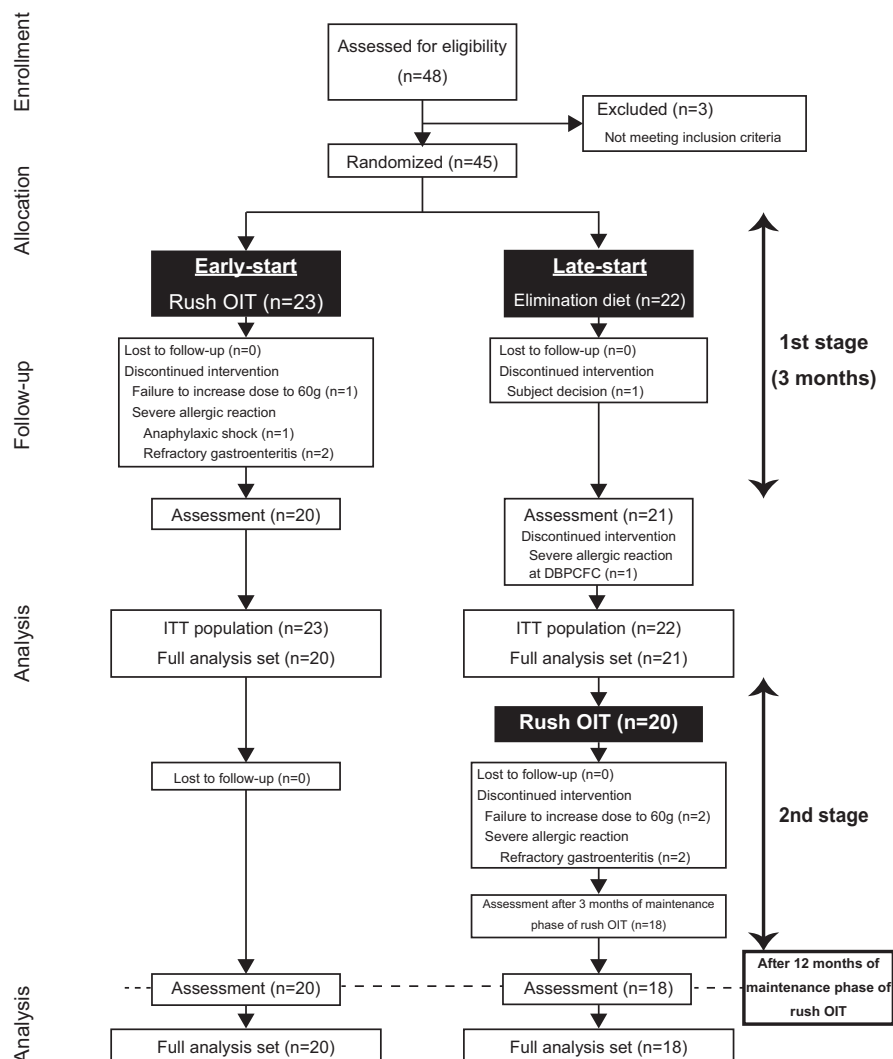


Fig. 1. A flow diagram of the present study. OIT, oral immunotherapy; DBPCFC, double-blind, placebo-controlled food challenge; ITT, intention-to-treat.

Desensitization to egg, the intake of egg dishes in daily life and school-life, and changes in the QOL of the guardians during 12 months of rOIT

We analyzed the whole study population, including both the early-start and late-start group members, to investigate the TD of EWP after 2 weeks of elimination diet following 12 months of rOIT. After 3 months of rOIT, 100% of the participants had already achieved a TD of EWP of ≥ 1000 mg (Table 3). Moreover, desensitization

was achieved in almost all of the participants (the TD was more than before starting rOIT), even after 2 weeks of elimination diet. However, in some participants the TD was <1000 mg, suggesting that the desensitization might have been weakened during the 2 weeks of the elimination diet.

As our rOIT allowed the participants to consume egg dishes on the days in which the participants did not receive rOIT in the maintenance phase of therapy, 74.2% of the participants were able

Table 1

The baseline demographics and clinical characteristics of the participants.

	Early-start group (n = 23)	Late-start group (n = 22)	p value
Age (years, median [range])	7 (5–12)	8 (5–13)	0.42
Sex (female)	26.1%	27.3%	0.93
Total IgE (IU/mL, median [range])	683.6 (122.4–8537.1)	774.5 (56.3–5809.8)	0.62
Serum sIgE to egg white [U _A /mL, median (range)]	35.9 (1.2–201.6)	32.6 (2.4–367.8)	0.98
Serum sIgE to ovomucoid [U _A /mL, median (range)]	22.3 (0.6–236.0)	25.4 (1.2–227.1)	0.71
Skin prick test to egg white [wheal, mm, median (range)]	13.0 (4.4–26.0)	12.0 (7.0–24.0)	0.62
Bronchial asthma	65.2%	59.1%	0.67
Atopic dermatitis	82.6%	77.3%	0.65
Duration of egg elimination (years, median [range])	7 (5–12)	8 (5–13)	0.42
DBPCFC			
TD of EWP (mg, median [range])	100 (10–500)	100 (10–500)	0.36
The worst symptom severity (grade, median [range])	3 (2–4)	3 (2–4)	0.94

DBPCFC, double-blind, placebo-controlled food challenge; TD, threshold dose; EWP, egg white powder.

Table 2

Comparison of the outcomes during the 1st stage.

Endpoint	Number (%)		Relative risk (95% CI)	p Value
	Early-start group (n = 23)	Late-start group (n = 22)		
Primary endpoint				
<i>Desensitization</i>				
Achieved an increase in the TD of EWP	20 (87.0)	5 (22.7)	3.83 (1.74–8.40)	<0.001
Secondary endpoints				
<i>Desensitization</i>				
Achieved a TD of EWP of ≥ 1000 mg	20 (87.0)	0 (0.0)	39.29 (2.52–612.50) [†]	<0.001
<i>QOL of the guardians</i>				
Achieved an improvement of ≥ 1 point in the QOL score	15 (65.2)	12 (54.6)	1.20 (0.74–1.94)	0.55
Achieved an improvement of ≥ 10 points in the QOL score	15 (65.2)	7 (31.8)	2.05 (1.04–4.05)	0.04
<i>Serum egg-specific immunoglobulin</i>				
Achieved a decrease of IgE to ovomucoid	10 (43.5)	13 (59.1)	0.74 (0.41–1.32)	0.38
Achieved an increase of IgG4 to ovomucoid	22 (95.7)	10 (45.5)	2.10 (1.32–3.35)	<0.001
<i>Skin prick test</i>				
Achieved a decrease of wheal size to egg white	14 (60.9)	8 (36.4)	1.67 (0.88–3.18)	0.14
Achieved a ≥ 5 mm decrease in the wheal size to egg white	13 (56.5)	0 (0)	25.88 (1.63–410.53) [†]	<0.001
<i>Basophil activation test</i>				
Achieved a decrease in the ratio of activated basophils	15 (65.2)	10 (45.5)	1.43 (0.83–2.48)	0.24

TD, threshold dose; EWP, egg white powder; QOL, quality of life.

[†] Adjusted relative risk.

to consume egg dishes at home and 28.9% of the participants were able to consume egg dishes at school (Table 4). The ratio of egg dishes consumed at home and at school did not differ to a statistically significant extent between the early-start and late-start groups.

We evaluated the QOL of the guardians during the rOIT and found that the QOL was significantly improved, even after 3 months of rOIT (median, 13 points improvement, $p < 0.05$), and that the improvement was sustained, even after 12 months of the maintenance phase of rOIT (median, 14.5 points improvement, $p < 0.05$) (Fig. 2).

The changes in the immunological features during 12 months of rOIT

Similarly to previous reports,^{13,14} we found a significant decrease in the serum-specific IgE levels to ovomucoid (median, 6.22–19.1 U_A/mL, $p < 0.05$, Fig. 3A), the percentage of CD203c⁺ basophils upon stimulation with egg white (median, 9.26%–94.4%, $p < 0.05$, Fig. 3C), and the wheal size to egg white (median, 10.0–11.5 mm, $p < 0.05$, Fig. 3D) during the 12-month period of rOIT. On the other hand, the serum-specific IgG4 levels to ovomucoid (median, 0.26–7.55 mg_A/L, $p < 0.05$, Fig. 3B) significantly increased during the 12-month period of rOIT.

Harmful effects

In the early-start group, approximately 80% of the participants showed an allergic reaction during the first stage of the study, whereas none of the patients in the late-start group experienced an

allergic reaction (Table 5). However, the reactions were treated with anti-histamine and/or steroids, and there was no significant increase in the use of adrenaline injections in the early-start group. The allergic reactions in the early-start group mainly occurred in the skin, the gastrointestinal tract, or the respiratory tract; 1 participant who experienced anaphylactic shock and 2 participants who experienced refractory gastroenteritis, who not able to continue rOIT and were withdrawn from the study. By the end of the 2nd stage, 5 participants (11.1%) were unable to continue rOIT due to allergic reactions and were withdrawn from the study (Fig. 1).

Discussion

In this study, we demonstrated that the rOIT induced not only desensitization to egg but also improved the QOL of the guardians. To the best of our knowledge, this is the first report to show that rOIT for egg allergy improved the QOL of guardians. Further studies are needed to clarify the impact of OIT on the QOL in both patients and their family members and to consider the clinical applications of this therapy in the future.

Limitations

The present study was associated with some limitations. Firstly, we only evaluated the efficacy and safety of rOIT in a 3-month

Table 3

Desensitization to egg by rOIT.

	Whole study population (n = 38)
After 3 months of rOIT	
TD of EWP was more than before starting rOIT	38 (100%)
Achieved a TD of EWP of ≥ 1000 mg	38 (100%)
After 2 weeks of elimination diet following 12 months of the maintenance phase of rOIT	
TD of EWP was more than before starting rOIT	37 (97.4%)
Achieved a TD of EWP of ≥ 1000 mg	31 (81.6%)

rOIT, rush oral immunotherapy; TD, threshold dose; EWP, egg white powder.

Table 4

The consumption of egg dishes by participants.

	Consumed egg dishes at home (n = 38)	Consumed egg dishes at school (n = 38)
After 3 months of rOIT	23 (74.2%)	11 (28.9%)
Early-start group (n = 20)	10 (50.0%)	4 (20.0%)
Late-start group (n = 18)	13 (72.2%)	7 (38.9%)
After 12 months of the maintenance phase of rOIT	31 (81.6%)	18 (47.4%)
Early-start group (n = 20)	14 (70.0%)	7 (35.0%)
Late-start group (n = 18)	17 (94.4%)	11 (61.1%)

rOIT, rush oral immunotherapy.

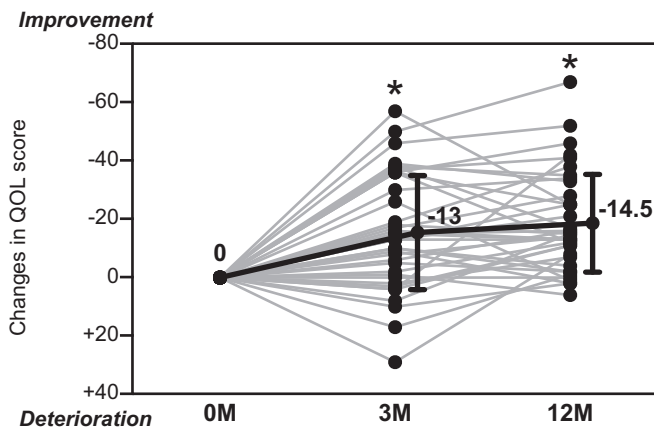


Fig. 2. Changes in the QOL score during 12 months of rOIT. The changes in the QOL score of the guardians from pre-rOIT (0M) were significantly lower (improvement) after 3 months and 12 months of rOIT. The values are shown as the median and interquartile range. *A significant difference in comparison to pre-rOIT ($p < 0.05$). rOIT, rush oral immunotherapy; QOL, quality of life; M, month(s).

period (the 1st period) and not over a longer period because we selected the delayed-start study design to allow more patients to receive the active treatment. Another methodological limitation was that TDs of EWP of >1000 mg could not be measured due to the DBPCFC protocol. Thus, we could not clarify whether the TD was decreased after 2 weeks of elimination following 12 months of rOIT. Furthermore, we found a participation bias regarding the QOL of the guardians (Table 2), which might have resulted from the patients joining the clinical trial and have been based on the hope that their child's food allergy would be cured. To clarify the impact of any participation bias, we analyzed the changes in the QOL separately in each group. We found that the change in the QOL of the early-start group improved after the initiation of rOIT

(Supplementary Fig. 2). On the other hand, the changes in the QOL of the late-start group also improved after the initiation of rOIT (at the end of the first stage), but not before rOIT (during the first stage), suggesting that the improvement in the QOL might have been due to rOIT and not a participation bias. In addition, we could evaluate the effects of rOIT on the QOL based on the changes in the QOL score to rule out any potential participation bias. The FAQL-PB that was used in this study was originally written in English and was translated to Japanese with the author's permission. To date, there is a well-validated Japanese questionnaire on the food allergy-related QOL.¹⁵ However, when we started this RCT in 2010–2011, the validated Japanese questionnaire on the food allergy-related QOL was not available. Finally, QOL questionnaires, including the Food Allergy Quality of Life – Parental Burden Questionnaire that was used in the present study used, the lack of questions related to the burden associated with therapy for food allergies, such as watching harmful events caused by OIT or the duty to systematically feed their children foods to which they are allergic at home. Thus, the existing questionnaire is considered to have been suitable for assessing the QOL of the guardians whose children underwent OIT.

Generalizability

Different circumstances, such as eating customs, food labeling rules, and accessibility to emergency care might affect the generalizability of our findings in terms of the improvement of QOL. The rOIT for other foods such as milk or wheat might be associated with different effects and different levels of safety.

Interpretation

Similarly to previous studies,⁷ rOIT had a substantial benefit in terms of desensitization in the present study (RR 3.83, 95% CI

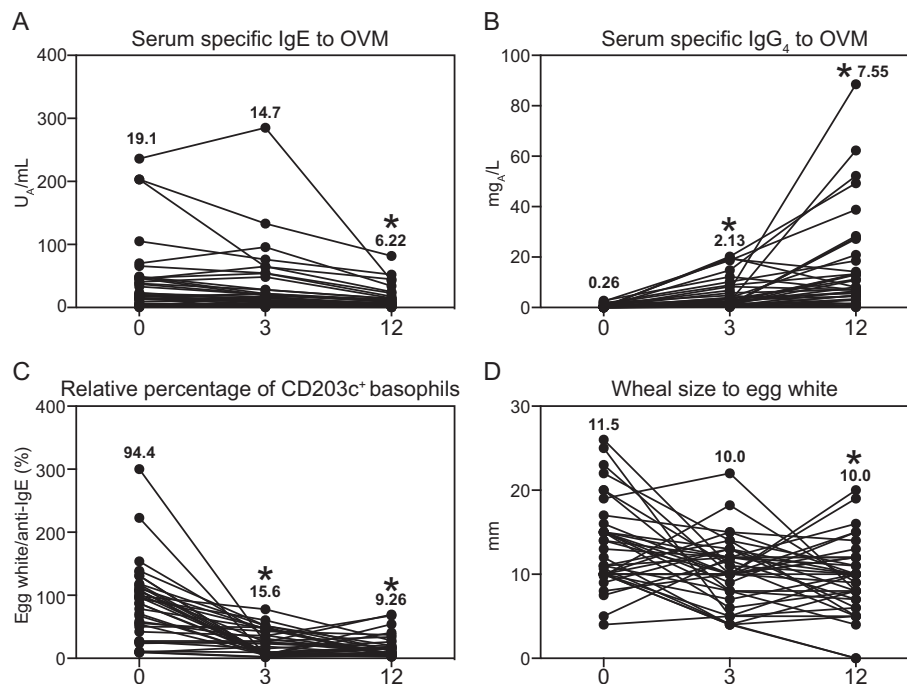


Fig. 3. The changes in the immunological features during 12 months of rOIT. (A) The serum-specific IgE levels to OVM were significantly decreased after 12 months of rOIT. (B) The serum-specific IgG₄ levels to OVM were significantly increased after 3 and 12 months of rOIT. (C) The relative percentage of CD203c⁺ basophils upon stimulation with egg white to the relative percentage of CD203c⁺ basophils upon stimulation with anti-IgE were significantly decreased after 3 and 12 months of rOIT. (D) The wheal size to egg white was significantly decreased after 12 months of rOIT. The values are shown as the median. *Significant difference in comparison to pre-rOIT (0M) ($p < 0.05$). rOIT, rush oral immunotherapy; OVM, ovomucoid; M, month(s).

Table 5

The harmful effects during the 1st stage.

Harmful effects	Number (%)		Modified relative risk (95% CI)	p Value
	Early-start group (n = 23)	Late-start group (n = 22)		
All allergic reactions	19 (82.6)	0 (0)	37.4 (2.4–583.6)	<0.001
Adrenaline injection	2 (8.7)	0 (0)	4.79 (0.24–94.33)	0.49
Skin				
Grade 1 and 2	12 (52.2)	0 (0)	23.96 (1.50–381.69)	<0.001
GI tract				
Grade 1 and 2	17 (73.9)	0 (0)	33.54 (2.14–525.93)	<0.001
Grade ≥3	10 (43.5)	0 (0)	20.13 (1.25–324.02)	<0.001
Respiratory tract effects				
Grade 1 and 2	12 (52.2)	0 (0)	23.96 (1.50–381.69)	<0.001
Grade ≥3	10 (43.5)	0 (0)	20.13 (1.25–324.02)	<0.001
Cardiovascular effects				
Grade ≥4	1 (4.3)	0 (0)	2.88 (0.12–67.03)	1.00
Neurological effects				
Grade 5	0 (0)	0 (0)	0.96 (0.02–46.32)	1.00

GI, gastrointestinal.

1.74–8.40). Surprisingly, 97.4% of the participants of the whole study population achieved sustained unresponsiveness at 2-weeks after the discontinuation of rOIT, suggesting that the beneficial effects may be maintained by consuming an egg-containing diet in daily life.

In terms of harm, rOIT was associated with a significant increase in the incidence of allergic reactions (RR 37.4, 95% CI 2.4–583.6). Severe reactions requiring adrenaline injection occurred in 11.6% of the patients (n = 5, 3 in the build-up phase, 2 in the maintenance phase) of the participants who received rOIT; however, 4 of the participants were able to continue rOIT. On the other hand, 9.3% (n = 4) of the participants who experienced refractory gastroenteritis were not able to continue rOIT. Although we did not perform endoscopy to investigate the cause of gastroenteritis in these cases, the refractory GI tract symptoms may have occurred due to eosinophilic esophagitis or eosinophilic gastroenteritis, as was reported in previous studies.^{16,17} Further studies are needed to clarify how to predict or prevent adverse effects.

In terms of QOL, a few RCTs of OIT for peanut allergy reported that the disease-specific QOL of patients and their families was improved.^{8,9} Thus, this is the first study to report that rOIT for egg allergy improved the QOL of guardians. To date, most studies on OIT for food allergy have focused on the efficacy and the safety. However, other outcomes related to the improvement of daily life in food allergy patients and their families should be further investigated. In our study, the QOL of the guardians was significantly improved by rOIT. This may have been due to the rOIT protocol which allowed the patients to consume egg dishes in their daily life. On the other hand, some of the participants in the present study disliked eggs, presumably due to the long-term elimination of egg before the study, oral discomfort, or harmful events caused by rOIT. This might have worsened the QOL of the guardians, and OIT using a low maintenance dose might be appropriate for such patients. Due to small number of the participants, we could not determine the factors that were associated with improvements in the QOL in the present study. Studies to clarify these factors are needed to determine the appropriate targets for therapy.

In conclusion, our study found that the rOIT induced desensitization to egg and improved the QOL of guardians. Further studies should be performed to clarify the impact of OIT on the QOL of patients.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.alit.2017.07.007>.

Conflict of interest

The authors have no conflict of interest to declare.

Authors' contributions

NIN contributed to the conduct of the study, collected data, and wrote the manuscript. YI performed the statistical analysis and interpretation of the results, and wrote the manuscript. MN collected data and performed interpretation of the results. TF, NS and TI contributed to the study design and the conduct of the study.

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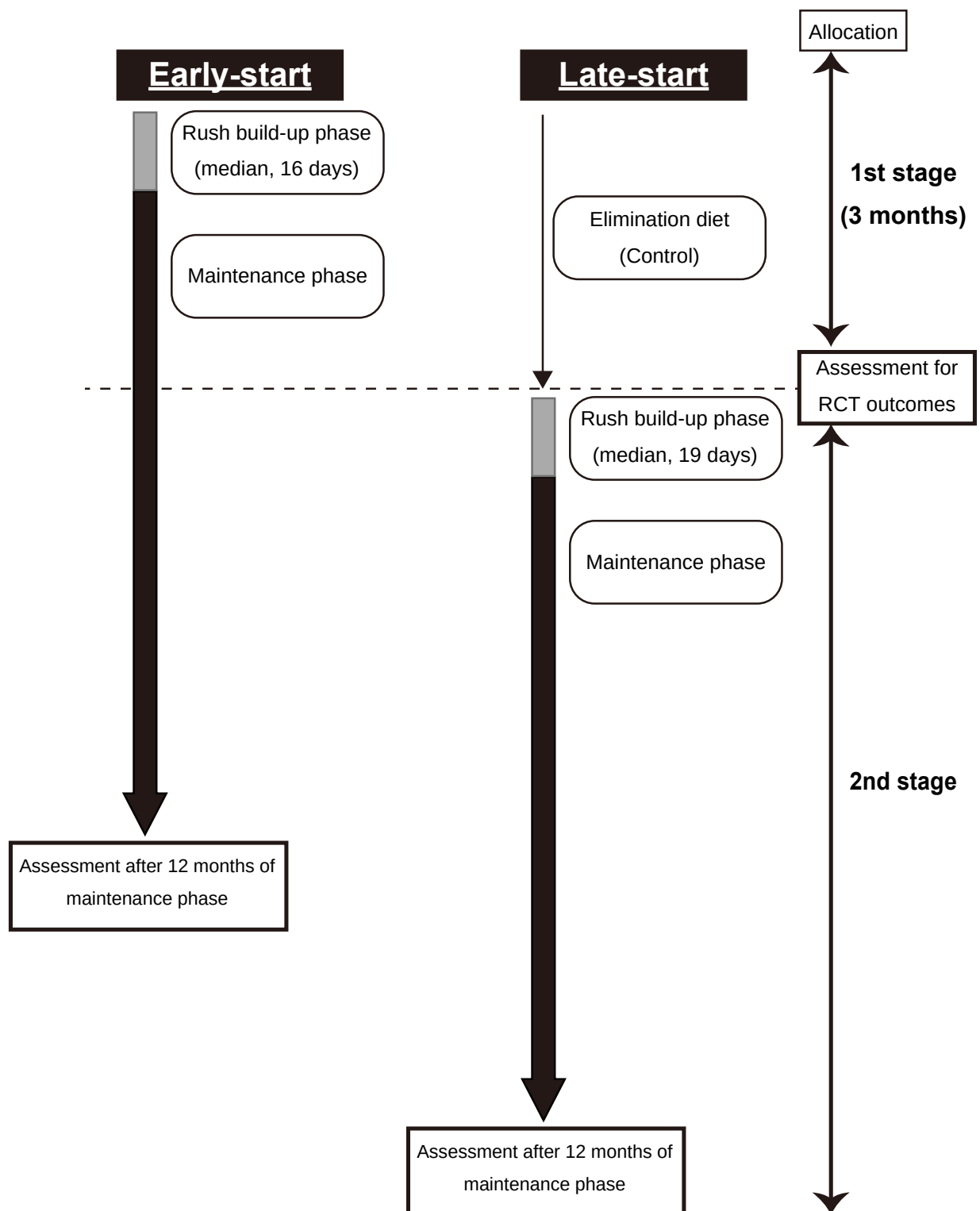
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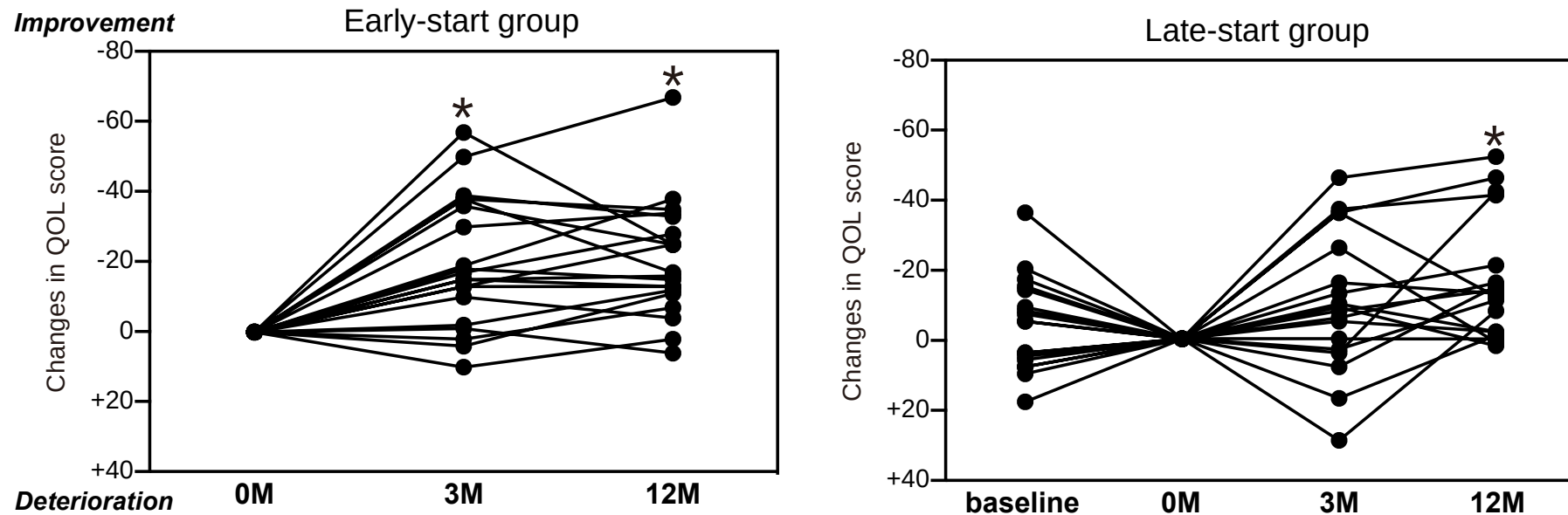
Supplementary Table 1. The grades of allergic reactions.

Severity	MILD		MODERATE		SEVERE
Grade	1	2	3	4	5
Skin	Localized skin rash	Generalized skin rash			
GI tract	Oral pruritus	- Abdominal pain - Nausea	- Single vomiting - Single diarrhea	- Recurrent vomiting - Recurrent diarrhea	Loss of bowel control
Respiratory tract	Rhinorrhea	- Sensation of throat pruritus or tightness - Cough	- Continuous coughing - Wheezing	- Coughing - Wheezing - Cyanosis together with dyspnea	Respiratory arrest
Cardiovascular				Hypotension (15% decrease in BP or ≥20mmHg decrease in BP)	- Bradycardia - Cardiac arrest
Neurological					Loss consciousness

GI, Gastrointestinal.



Supplementary Fig. 1. schematic illustration of the rush build-up phase and the maintenance phase in each group .



Supplementary Fig. 2. The changes in the QOL score during 12 months of rOIT in each group.

In the early-start group, the change in the QOL score of the guardians from pre-rOIT (0M) was significantly lower (improvement) after 3 months and 12 months of rOIT. In the late-start group, the QOL score of the guardians did not change to a statistically significant extent under the elimination diet (from baseline to 0M), while the QOL was significantly improved after 12 months of rOIT.