



Contents lists available at ScienceDirect

Allergology International

journal homepage: <http://www.elsevier.com/locate/alit>

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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ARTICLE INFO

Article history:

Received 11 April 2017

Received in revised form

29 June 2017

Accepted 4 July 2017

Available online xxx

Keywords:

Desensitization

Food allergy

Guardians

Oral immunotherapy

Quality of life

Abbreviations:

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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Peer review under responsibility of Japanese Society of Allergology.

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<http://dx.doi.org/10.1016/j.alit.2017.07.007>

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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

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