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Original article

Better management of wheat allergy using a very low-dose food challenge: A retrospective study

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EAACI	European Academy of Allergy and Clinical Immunology
OFC	Oral food challenge
OIT	Oral immunotherapy
VL	Very low-dose

ABSTRACT

Background: Low-dose reactive wheat-allergic children are at a high risk of a positive oral food challenge (OFC). The present study aimed to evaluate whether the results of a very low-dose (VL) OFC would contribute to better wheat allergy management in this population.
Methods: We retrospectively reviewed wheat-allergic subjects who underwent a VL OFC with 2 g of udon noodles (equivalent to 53 mg of wheat protein) and had a previous allergic reaction to <15 g of udon noodles (equivalent to 400 mg of wheat protein) within 2 years before the OFC. Subjects who passed the OFC were defined as VL tolerant; those who failed were considered VL reactive. In VL tolerant subjects, the dose was increased to 15 g of udon noodles either during an OFC in our hospital or gradually at home.
Results: Of the 57 included subjects (median age, 2.9 years; range, 1.0–11.8 years), 32 (56%) were VL tolerant and 25 (44%) were VL reactive. Most reactions during the OFC could be treated with an antihistamine and/or a nebulized β2 agonist. VL tolerant subjects consumed 2 g of udon noodles or a seasoning containing wheat. Within a year after the OFC, 18 VL tolerant subjects (56%), but no VL reactive subjects, were able to consume 15 g of udon noodles ($p < 0.001$).
Conclusions: A VL OFC can shift the management of some low-dose reactive wheat-allergic children from complete avoidance to partial wheat intake.

Introduction

Immunoglobulin (Ig) E-mediated wheat allergy is the third-most common food allergy in Japan.[1] A review of the natural history of wheat allergy reported that 29%, 56%, and 65% of children outgrow such allergies by age 4, 8, and 12 years, respectively.[2,3] However, many children continue to suffer from wheat allergy, and an oral food challenge (OFC) is therefore needed to assess the achievement of tolerance.[4] These challenges must be conducted carefully in low-dose reactive wheat-allergic children, who are at a high risk of a positive OFC and react severely to high-dose intakes.[5,6]

Oral immunotherapy (OIT), which reportedly contributes to desensitization or threshold elevation in wheat-allergic children,[7,8] is a possible approach for the management of wheat allergy. However, this process might be impractical or inconvenient in real life because of the need for daily ingestion and risk of possible adverse reactions.[9]

Baked egg and baked milk have been used as approaches for the management of hen egg allergy and cow's milk allergy, respectively.[10,11] On the other hand, wheat is usually consumed in a cooked form, and allergenicity was not found to differ significantly between raw and cooked forms of wheat.[12]

We previously reported that a very low-dose (VL) OFC with cow's milk provided better management in patients with low-dose reactive cow's milk allergy.[13] Therefore, we decided to test a VL OFC with wheat for wheat allergy. To determine whether a VL OFC with wheat was as effective for wheat allergy as a VL OFC with cow's milk for cow's milk allergy, we performed a VL OFC (2 g of udon noodles, equivalent to 53 mg of wheat protein) and wheat dose progression in wheat-allergic children who had experienced a previous reaction to <15 g of udon noodles (equivalent to 400 mg of wheat protein) based on our daily practice.

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Methods

Study design

We retrospectively reviewed subjects with low-dose wheat reactions who underwent a VL OFC involving 2 g of udon noodles. Subjects who passed the VL OFC were defined as VL tolerant, and those who failed the VL OFC were defined as VL reactive.

The results of the VL OFC are presented as the OFC positive rate, as well as symptoms and treatments administered during the OFC. The results of the wheat dose progression in our daily practice during a 1-year period after the OFC were compared between the VL tolerant and VL reactive subjects according to the time needed to reach an intake of 15 g of udon noodles.

Informed consent for the OFC and data publication was obtained from the children's guardians. This study was approved by the Sagamihara National Hospital Ethics Committee and was conducted in accordance with the Declaration of Helsinki. The research plan was posted at Sagamihara National Hospital. However, because this study was retrospective, registration in an internationally certified registry was not required.

Subject selection

The eligible subjects were children who underwent VL OFC between July 2012 and January 2014, had a previous allergic reaction to <15 g of udon noodles within the 2 years before the VL OFC (median, 9.3 months; range, 1.5–23.2 months), and had a positive wheat-specific IgE test result. Previous allergic reactions were defined as immediate reactions if they occurred within 2 h after ingesting wheat. Worsening of eczema or asthma after ingesting wheat was not included in the immediate reactions. If previous allergic reactions occurred because of accidental ingestion, wheat doses were calculated using a conversion table constructed by the research dieticians.

Assessment of baseline characteristics

The attending physician was responsible for diagnoses of food allergies, eczema, asthma, and allergic rhino-conjunctivitis. Anaphylaxis was defined according to the criteria proposed by Simons *et al.*[14]

Laboratory testing

For all subjects, wheat-specific IgE levels were assessed using the ImmunoCAP assay system (Thermo Fisher Scientific, Uppsala, Sweden), and a level >0.35 kilounits of allergen-specific IgE (kUA)/L was considered positive. The median time between the laboratory test and VL OFC was 3.2 months (range, 0.0–18.4 months).

Oral food challenge protocol

The challenge food used in the VL OFC was 2 g of udon noodles (equivalent to 53 mg of wheat protein). Udon noodles are a traditional Japanese food prepared by boiling a mixture of wheat flour, water, and salt for 1 min.

OFCs were performed openly under physician observation at Sagamihara National Hospital. One quarter of the VL OFC challenge food was administered initially, and the remaining three quarters were administered 60 min later. The OFC was concluded when a quantity of wheat sufficient to cause moderate or severe symptoms (generalized urticaria, continuous coughing, moderate or severe abdominal pain, vomiting, or diarrhoea) had been consumed. If mild objective symptoms (localized urticaria or intermittent coughing) appeared during the OFC, the subject was carefully monitored to detect any worsening of symptoms. If the mild objective symptoms disappeared within 30 min, the OFC was continued. When an adverse reaction occurred, treatment (antihistamine, nebulized β2 agonist, steroids, or adrenaline) was administered based on the European Academy of Allergy and Clinical Immunology (EAACI) food allergy and anaphylaxis guidelines.[15]

Wheat dose progression and follow-up

Subjects who passed the VL OFC were advised to consume 2 g of udon noodles or a seasoning containing wheat at least once weekly while at home. One to 3 months after passing the OFC, the wheat dose was increased to 15 g of udon noodles either during an OFC at our hospital or gradually at home. With the latter method, the udon noodle dose was increased by 1 g every few ingestions. If adverse reactions appeared, the previous dose was repeated. When the previous dose was passed, the scheduled increase was attempted. Subjects who failed the VL OFC underwent a second OFC at least 6 months after the first OFC.

We prescribed antihistamines for all subjects, adrenaline autoinjectors for subjects with a history of anaphylaxis, and other medications depending on complications. All subjects received instructions on when and how to administer emergency medications and visit the emergency department.

Statistical analysis

Characteristics at the time of the VL OFC were compared between the VL tolerant and VL reactive subjects, as well as between VL tolerant subjects who achieved a dose of 15 g of udon noodles (15 g tolerant) and VL tolerant subjects who failed an OFC with 15 g of udon noodles (15 g reactive) within 1 year after the VL OFC using the Mann–Whitney test for continuous variables (expressed as medians and ranges) and the chi-square or Fisher's exact test for categorical variables (expressed as numbers and percentages).

Wheat dose progression was measured as the time required to reach the consumption of 15 g of udon noodles. Kaplan–Meier curves were generated to depict changes among the VL tolerant and VL reactive subjects. Differences were estimated using the log-rank test.

SPSS version 20 (IBM Corp, Armonk, NY, USA) was used for all analyses.

Results

Baseline subject characteristics

Of the 83 subjects who underwent the VL OFC between July 2012 and January 2014, 23 subjects were excluded for a previous allergic reaction to wheat more than 2 years prior, and 3 were excluded for a previous reaction to >15 g of udon noodles within the previous 2 years; a total of 57 subjects (median age, 2.9 years; range, 1.0–11.8 years) remained in the analyses (Fig. 1). The median wheat-specific IgE level was 26.9 kUA/L (range, 0.63–1520 kUA/L), and the median ω5-specific IgE level was 1.5 kUA/L (range, <0.10–65.3 kUA/L) (Table 1). Of the baseline subject characteristics, the VL tolerant (n = 32, 56%) and VL reactive (n = 25, 44%) subjects differed significantly with regard to a history of anaphylaxis to wheat, wheat-specific IgE levels, and ω5-specific IgE levels (Table 1).

The subjects' previous allergic reactions had been caused by accidental ingestion (56%) or an OFC with wheat (44%). The median threshold dose at the previous OFC with wheat was 8.0 g (range, 2.0–15.0 g) of udon noodles (Table 2). The threshold dose in the previous OFC with wheat was higher among VL tolerant subjects