Allergology International 64 (2015) 272–276

Contents lists available at ScienceDirect

Allergology International

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

Original article

# Better management of cow's milk allergy using a very low dose food challenge test: A retrospective study

Yu Okada [a], Noriyuki Yanagida [a], Sakura Sato [b], Motohiro Ebisawa [b, *]

[a] Department of Pediatrics, Sagamihara National Hospital, Kanagawa, Japan
[b] Department of Allergy, Clinical Research Center for Allergology and Rheumatology, Sagamihara National Hospital, Kanagawa, Japan

ARTICLE INFO

*Article history:*
Received 1 March 2015
Accepted 1 April 2015
Available online 8 May 2015

*Keywords:*
Milk hypersensitivity
Disease management
Food allergy
Food hypersensitivity
Specific IgE

*Abbreviations:*

| | |
|---|---|
| CM | cow's milk |
| EAACI | European Academy of Allergy and Clinical Immunology |
| OFC | oral food challenge |
| OIT | oral immunotherapy |
| VL | very low dose |

ABSTRACT

*Background:* Low dose reactive cow's milk (CM) allergic children are at high risk of persistent CM allergy and a positive oral food challenge (OFC). The present study aimed to evaluate if the results of a very low dose (VL) OFC with these children contributes to better management of CM allergy.
*Methods:* We retrospectively reviewed subjects with CM allergy who underwent a VL OFC with 3 mL heated CM and had a previous allergic reaction to <25 mL heated CM in the 2 years before the OFC. Subjects who passed the OFC were defined as VL tolerant, and subjects who failed were defined as VL reactive. VL tolerant subjects increased the dose to 25 mL heated CM either during an OFC in our hospital or gradually at home.
*Results:* Of the 83 subjects (median age, 4.3 years; range, 1.0–12.9 years) who were included, 41 (49.4%) were VL tolerant, and 42 (51.6%) were VL reactive. Thirty-nine VL reactive subjects had skin and/or respiratory symptoms during the OFC. Most reactions could be treated with an antihistamine and/or a nebulized β2 agonist. The VL tolerant subjects consumed 3 mL heated CM or 10 g butter. Within the year following the OFC, 18 VL tolerant subjects (45.0%), but none of the VL reactive subjects, were able to consume 25 mL heated CM ($p < 0.001$).
*Conclusions:* A VL OFC allows the management of some low dose reactive CM allergic children to change from complete avoidance to partial intake of CM.


## Introduction

IgE-mediated cow's milk (CM) allergy is a common food allergy in infancy.[1–3] Many children tend to outgrow a CM allergy in early childhood[4,5]: 50% by age 5 and 75% by the early teenage years based on a review of natural history.[4] However, some children continue to suffer from CM allergy, and an oral food challenge (OFC) is needed to assess the achievement of tolerance.[6] Low dose reactive CM allergic children are at a high risk of persistent CM allergy[5] and a positive OFC.[7] Because high dose intakes for these children cause severe reactions,[8] the OFC must be conducted carefully.

Baked milk[9,10] and milk oral immunotherapy (OIT)[11–13] are possible approaches for CM allergy. Because many CM allergic children tolerate baked milk,[9–11] it can improve the dietary variety in these children, who then generally have a good prognosis with their unheated CM allergy.[12] However, the challenge food for baked milk contains 0.5–1.3 g CM protein (equivalent to 15–40 mL CM),[9–11] and children who react to baked milk avoid CM completely.[12]

Milk OIT for CM allergic children reportedly contributes to desensitization or threshold elevation,[13–15] but it might be impractical or inconvenient in real life because of the need for daily ingestion and risk of possible adverse reactions.[13] In addition, it is difficult to achieve desensitization with milk OIT for low dose reactive CM allergic children, and there is a high rate of adverse reactions.[14,15]

Therefore, to identify strategies for better management of CM allergy, we performed a very low dose (VL) OFC (3 mL heated CM) and CM dose progression in CM allergic children who had experienced a previous reaction to <25 mL heated CM, based on our daily practice.

## Methods

### Study design

We retrospectively reviewed subjects with low dose CM reactions who underwent a VL OFC, which involves 3 mL heated CM

* Corresponding author. Department of Allergy, Clinical Research Center for Allergology and Rheumatology, Sagamihara National Hospital, 18-1, Sakuradai, Minami-ku, Sagamihara, Kanagawa 252-0392, Japan.
*E-mail address:* m-ebisawa@sagamihara-hosp.gr.jp (M. Ebisawa).
Peer review under responsibility of Japanese Society of Allergology.

http://dx.doi.org/10.1016/j.alit.2015.04.002

(equivalent to 100 mg CM protein). Subjects who passed the VL OFC were defined as VL tolerant, and subjects who failed the VL OFC were defined as VL reactive.

The results of the VL OFC are presented as the OFC positive rate and symptoms and treatments administered during the OFC. The results of CM dose progression based on our daily practice during the year after the OFC are compared using the time to reach 25 mL heated CM between the VL tolerant and VL reactive subjects.

Informed consent for the OFC and publication of the data 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*

Eligible subjects were children who underwent VL OFC between July 2012 and December 2013, had a previous allergic reaction to <25 mL of heated CM (equivalent to 850 mg CM protein) within the 2 years before the VL OFC (median, 12.2 months; range, 0.6–23.9 months) and had a positive CM-specific IgE. Previous allergic reactions were defined as immediate reactions if they occurred within 2 h after ingesting CM. Worsening of eczema or asthma after ingesting CM was not included in the immediate reactions. If previous allergic reactions occurred because of accidental ingestion, CM doses were calculated based on a conversion table constructed by the research dieticians.

### *Assessment of baseline characteristics*

The attending physician was responsible for diagnoses of other food allergies, eczema, asthma, and allergic rhino-conjunctivitis. Anaphylaxis was defined as fulfilling the criteria proposed by Simons et al.[16]

### *Laboratory test*

CM-specific IgE was assessed using the ImmunoCAP assay system (Thermo Fisher Scientific, Uppsala, Sweden) for all subjects, and >0.35 kUA/L was considered positive. The median time between the laboratory test and VL OFC was 4.0 months (range, 0.0–22.5 months).

### *Oral food challenge protocol*

The challenge food used in the VL OFC was pumpkin cake containing CM, which was prepared by mixing 3 mL CM, 3 g pumpkin, 2 g sorghum bicolor, 1 g sugar, 0.02 g baking soda, and 1 mL water. The mixture was heated to 90 °C for 1.5 min in a 1000-W microwave. For the OFC with 25 mL heated CM, we increased the ingredients by approximately 8 times the amount for the VL OFC challenge food.

OFCs were performed openly under physician observation at Sagamihara National Hospital. One-fourth of the VL OFC challenge food was administered initially, and the remaining three-fourths was administered 60 min later. The OFC was concluded when a quantity of CM 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 Food Allergy and Clinical Immunology (EAACI) food allergy and anaphylaxis guidelines.[17]

### *Cow's milk dose progression and follow-up*

Subjects who passed the VL OFC were advised to consume a food containing 3 mL heated CM or 10 g butter (equivalent to 2.9 mL CM[18]) at home at least once a week. One to three months after the OFC was passed, the CM dose was increased to 25 mL heated CM either during an OFC in our hospital or gradually at home. With the latter method, the heated CM dose was increased by 1 mL every few consumptions. 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 from the first OFC.

We prescribed antihistamines for all subjects, adrenaline autoinjectors for the 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*

Differences in characteristics at the time of the VL OFC were compared between the VL tolerant and VL reactive subjects using Mann–Whitney tests for continuous variables (expressed as median and range) and chi-square or Fischer's exact tests for categorical variables (expressed as number and percentage).

CM dose progression was measured as the time to reach consumption of 25 mL heated CM. Kaplan–Meier curves were generated to depict the changes for the VL tolerant and VL reactive subjects. The 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 131 subjects who underwent the VL OFC between July 2012 and December 2013, 48 subjects were excluded for a previous allergic reaction to CM more than 2 years prior, resulting in 83 subjects (median age, 4.3 years; range, 1.0–12.9 years) in the analyses (Fig. 1). The median CM-specific IgE level was 19.5 kUA/L (range, 0.66–284 kUA/L) (Table 1). Baseline subject characteristics were not significantly different between the VL tolerant (n = 41, 49.4%) and VL reactive (n = 42, 51.6%) subjects (Table 1).

The subjects' previous allergic reactions were caused by accidental ingestion (61.4%) or an OFC with CM (38.6%). The median threshold dose at the previous OFC with CM was 12.5 mL (range, 3.0–25.0 mL) (Table 2). The threshold dose in the previous OFC with CM was higher in the VL tolerant subjects than in the VL reactive subjects, and rate of skin symptoms was lower in the VL tolerant subjects than in the VL reactive subjects (Table 2).

### *Results of the very low dose oral food challenge*

Respiratory symptoms were the most common symptom, occurring in 83.3% (n = 35) of the VL reactive subjects, followed by skin symptoms, occurring in 81.0% (n = 34) of the VL reactive subjects. The majority of reactions were treated with antihistamines and/or nebulized β2 agonists. Among the 35 subjects with