



Original article

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

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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 β_2 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.

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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 allergy⁵ 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

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(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 β 2 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 CM¹⁸) 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 auto-injectors 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 β 2 agonists. Among the 35 subjects with

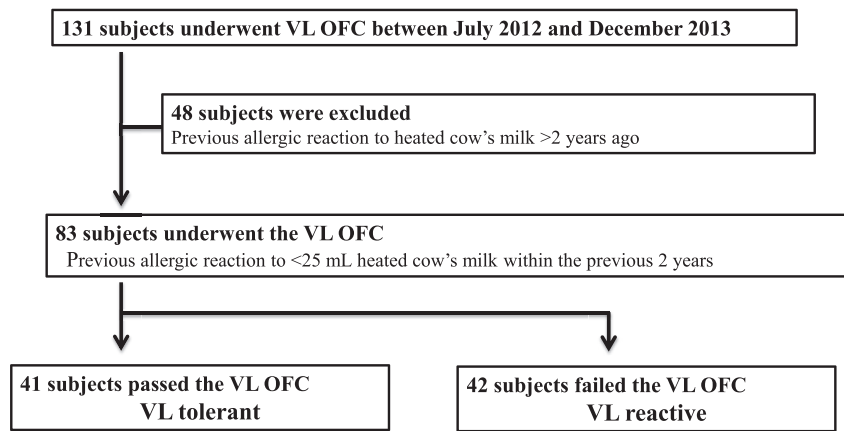


Fig. 1. Flowchart of enrolled subjects to assess the use of an oral food challenge (OFC) for cow's milk allergies. The VL OFC was conducted with 3 mL heated cow's milk. VL, very low dose; OFC, oral food challenge.

respiratory symptoms, 4 (11.4%) received only antihistamines, 27 (77.2%) received 1 dose of a nebulized β_2 agonist, 2 (5.7%) received 2 doses of nebulized β_2 agonist, and 2 (5.7%) received 1 dose of adrenaline. One subject received 1 dose of adrenaline for generalized urticaria with agitation (Table 3).

Cow's milk dose progression based on our daily practice within the year after the very low dose oral food challenge

Of the VL tolerant subjects, 14 underwent an OFC with 25 mL heated CM, and 9 of these subjects passed the OFC. The remaining 27 VL tolerant subjects gradually increased the CM dose at home, and 9 of these subjects reached 25 mL heated CM. Therefore, a total of 18 (45.0%) VL tolerant subjects reached 25 mL heated CM.

Of the VL reactive subjects, 24 underwent a second VL OFC, and only 3 subjects passed the second OFC. None (0.0%) of the VL reactive subjects reached 25 mL heated CM ($p < 0.001$) (Fig. 2).

Adverse reaction to cow's milk consumed at home

A 7-year-old boy had 2 reactionary episodes to 3 mL heated CM. In the first episode, moderate abdominal pain and persistent cough occurred after CM intake that was followed by walking. The reaction was treated with oral steroids and 1 dose of a nebulized β_2 agonist. In the second episode, mild abdominal pain occurred after CM intake. The subject did not consume more than 4 mL heated CM during the year after the VL OFC.

The heated CM dose could be increased in 40 subjects. Three subjects (7.5%) each had 1 reactionary episode to 4–25 mL heated CM. One subject had generalized urticaria, one subject had mild abdominal pain, and the remaining subject had an intermittent cough (Table 4). None of the adverse reactions required adrenaline or a visit to the emergency department. There was no worsening of eczema or asthma.

Discussion

To the best of our knowledge, this is the first study to indicate that VL OFC could be used to help manage food allergies in children with a low dose reactive CM allergy. Based on the OFC results, half of the children in the present study could begin consuming very low doses of CM products on a daily basis. Furthermore, approximately half of these VL-tolerant children could consume 25 mL heated CM within the year following the VL OFC.

Regarding the definition of low dose reactive CM used in the present study, we believe that it is appropriate because previous studies have used 25–30 mL CM for low dose OFCs^{19,20}; we defined low dose reactive CM allergy based on previous allergic reactions to <25 mL heated CM.

Cianferoni et al. reported that non-skin symptoms at the previous reaction are predictors of OFC.²¹ However, the frequency of skin symptoms at the previous reaction in the present study was lower in the VL tolerant subjects than in the VL reactive subjects. In the VL reactive subjects, 29 (72.5%) with skin symptom at the

Table 1

Baseline characteristics of subjects with cow's milk allergy who underwent a very low dose oral food challenge.

Characteristic	All subjects (n = 83)	VL tolerant (n = 41)	VL reactive (n = 42)	p value*
Age (years)	4.3 (1.0–12.9)	4.3 (1.0–12.9)	4.0 (1.2–8.2)	0.774
Male sex	52 (62.7)	24 (58.5)	28 (66.7)	0.444
History of anaphylaxis to CM	49 (59.0)	21 (51.2)	28 (66.7)	0.152
Other food allergy, current	58 (69.9)	27 (65.9)	31 (73.8)	0.430
Eczema, current	59 (71.1)	28 (68.3)	31 (73.8)	0.579
Asthma, current	24 (28.9)	11 (26.8)	13 (31.0)	0.679
Allergic rhino-conjunctivitis, current	20 (24.1)	8 (19.5)	12 (28.6)	0.335
Total IgE (kUA/L)	429 (28.5–7290)	521 (35.8–6090)	380 (28.5–7290)	0.906
CM-specific IgE (kUA/L)	19.5 (0.66–284)	19.7 (0.66–228)	19.2 (4.6–284)	0.112

*Comparisons between the VL tolerant and VL reactive subjects were conducted using Mann–Whitney tests for continuous variables or chi-square or Fischer's exact tests for categorical variables.

Values are reported as median (range) or n (%).

VL, very low dose; CM, cow's milk.

Table 2
Characteristics of previous allergic reaction to cow's milk.

Characteristic	All subjects (n = 83)	VL tolerant (n = 41)	VL reactive (n = 42)	p value*
Reason for previous allergic reaction to CM				
Accidental ingestion	51 (61.4)	25 (61.0)	26 (61.9)	0.931
OFC to CM	32 (38.6)	16 (39.0)	16 (38.1)	
Threshold dose at previous OFC to CM (mL)	12.5 (3.0–25.0) (n = 32)	22.5 (9.4–25.0) (n = 16)	9.7 (3.0–25.0) (n = 16)	0.002
Symptom at previous allergic reaction to CM				
Skin	73 (88.0)	33 (80.5)	40 (95.2)	0.040
Gastrointestinal	29 (34.9)	15 (36.6)	14 (33.3)	0.871
Respiratory	41 (49.4)	17 (41.5)	24 (57.1)	0.153
Cardiovascular	5 (6.0)	3 (7.3)	2 (4.8)	0.488
Anaphylaxis	49 (59.0)	21 (51.2)	28 (66.7)	0.152

*Comparisons between the VL tolerant and VL reactive subjects were conducted using Mann–Whitney tests for continuous variables or chi-square or Fischer's exact tests for categorical variables. Statistically significant p values (<0.05) are in bold. Values are reported as median (range) or n (%). VL, very low dose; CM, cow's milk; OFC, oral food challenge.

Table 3
Symptoms and administered treatments during the very low dose oral food challenge with cow's milk.

	VL reactive (n = 42)
Symptoms	
Skin (%)	34 (81.0)
Gastrointestinal (%)	13 (31.0)
Respiratory (%)	35 (83.3)
Cardiovascular (%)	0 (0.0)
Anaphylaxis (%)	30 (71.4)
Treatments	
Antihistamine (%)	41 (97.6)
β2 agonist, nebulized (%)	31 (73.8)
Steroids (%)	5 (11.9)
Adrenaline (%)	3 (7.1)

The very low dose (VL) reactive subjects failed the VL oral food challenge, which was conducted with 3 mL heated cow's milk.

previous reaction also had other symptoms, compared with 20 VL tolerant subjects (60.6%) with skin symptoms. Hence, it is possible that the severity of previous reactions and the threshold dose of a previous OFC with CM are predictors of VL OFC results.

Although many of the VL reactive subjects had skin and respiratory symptoms during the VL OFC, these reactions were treatable with antihistamines and/or nebulized β2 agonists. Compared with subjects who underwent an OFC with baked milk in previous

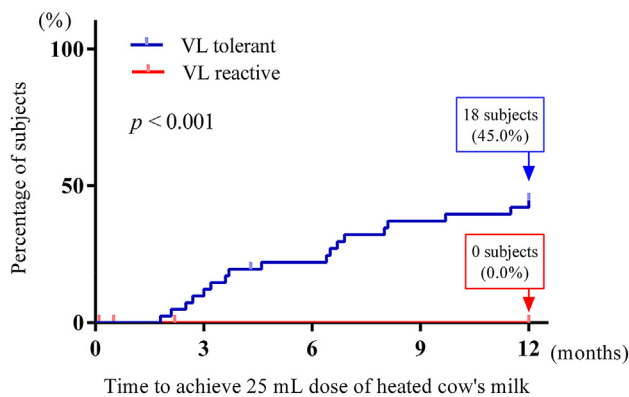


Fig. 2. Kaplan–Meier curves showing the time to achieve consumption of 25 mL heated cow's milk during the year after very low dose oral food challenge for cow's milk allergy. VL, very low dose; CM, cow's milk.

Table 4
Adverse reaction to heated cow's milk at home after passing the very low dose oral food challenge.

	VL tolerant	
	Very low dose (3 mL) (n = 41)	Dose escalation (4–25 mL) (n = 40 [†])
No. (%) of subjects	1 (2.4)	3 (7.5)
No. of adverse reactions	2	3
Skin	0	1
Gastrointestinal	2	1
Respiratory	1	1
Cardiovascular	0	0
Anaphylaxis	1	0

The very low dose (VL) tolerant subjects passed the VL oral food challenge, which was conducted with 3 mL heated cow's milk.

[†] One subject who had a reaction to 3 mL heated cow's milk at home did not consume >4 mL heated cow's milk within the year following the very low dose oral food challenge.

studies, the CM-specific IgE of our subjects was higher (median of subjects who failed the OFC in the present study, 19.2 kUA/L vs. 2.39–11.6 kUA/L), whereas the rate of adrenaline treatment in our subjects was lower (7% vs. 16–35%).^{9,10} Because of the high anaphylaxis rate, our adrenaline use may appear inappropriate. However, many respiratory symptoms were equivalent to mild wheezing as defined in the EAACI taskforce position paper,²² and most of the reactions were mild to moderate, even in those low dose reactive CM allergic children who failed the VL OFC.

Almost all of the VL tolerant subjects were able to safely consume 3 mL heated CM at home. One 7-year-old boy experienced moderate symptoms because of exercise, which is a known cofactor, in addition to infections and use of non-steroidal anti-inflammatory drugs.⁶ Although the children's guardians may need to aware of these cofactors, VL tolerant children can start to consume very low doses of CM and butter.

Previous studies suggest that VL intake several times per week improves food allergy. For example, Peters et al. reported that baked egg ingestion 1–4 times per month resulted in a higher resolution of raw egg allergy compared with no consumption.²³ Regarding VL intake, CM sublingual immunotherapy (0.1 mL of initial dose²⁴ and 3.7 mg of maintenance dose²⁵) increased the food challenge threshold approximately three-to sevenfold.^{24,25}

The limitations of our retrospective study include the lack of measurement of an accurate threshold using an OFC with a regular dose just before the VL OFC and the lack of a control group that did not undergo the VL OFC. An OFC with a regular dose in the control group would have provided information about the normal change in the food challenge threshold. We did not perform regular dose OFCs in the low dose reactive CM allergic children to avoid severe reactions. Based on the findings of the present study, we plan to conduct a prospective study of VL OFCs for these children. The heating method is another limitation. Our challenge food was heated to 90 °C for 1.5 min in a 1000-W microwave, while baked milk as a challenge food is baked at 180 °C for 20–30 min in an oven,^{9–11} which makes comparisons with baked milk studies difficult.

In conclusion, VL OFC helps to identify those low dose reactive CM allergic children who can shift from complete avoidance to partial intake of CM, providing better management of these children. Future randomized controlled trials are needed to determine if partial intake of CM improves CM allergy.

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Conflict of interest

The authors have no conflict of interest to declare.

Authors' contributions

YO performed research, analysed data, and wrote the paper. NY supervised YO's work. SS and ME contributed to the data analysis and the preparation and revision of the manuscript.

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