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Increased cow's milk protein–specific IgG4 levels after oral desensitization in 7- to 12-month-old infants

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ABSTRACT

Background: Cow's milk protein (CMP)-specific IgG4 responses and the efficacy of oral desensitization in infants with cow's milk allergy (CMA) warrant more clarification.

Objective: To explore whether CMP-specific IgG4 responses develop during infancy and whether regular CM exposure is efficacious for inducing a CMP-specific IgG4 response accompanying CM desensitization in 7- to 12-month-old infants.

Methods: CM-specific IgE and CMP (α -lactalbumin, β -lactoglobulin, and casein)-specific IgG4 levels were measured in 262 CM-sensitized children. Of these, 31 infants 7 to 12 months old with challenge-proved CMA were randomly assigned to oral desensitization or an elimination diet and evaluated 6 months later.

Results: CMP-specific IgG4 levels in 7- to 12-month-old infants were higher than in those younger than 6 months but comparable to those in children older than 12 months. CMP-specific IgG4 levels in 7- to 12-month-old infants with CMA were significantly lower than in those without CMA. Fourteen of 16 patients receiving oral desensitization could accept daily doses of 200 mL of CM, whereas all but 3 dropout patients receiving the elimination diet still showed allergic symptoms at the follow-up food challenge. In patients who became desensitized, CM-specific IgE levels were lower than at baseline, whereas CMP-specific IgG4 levels were significantly increased. In patients receiving the elimination diet, CM-specific IgE and CMP-specific IgG4 levels remained unchanged.

Conclusion: CMP-specific IgG4 responses did not develop sufficiently in 7- to 12-month-old infants with CMA. Oral desensitization in 7- to 12-month-old infants with CMA was associated with the upregulation of CMP-specific IgG4 responses accompanying the alleviation of CMA symptoms.

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Introduction

Cow's milk allergy (CMA) affects a significant portion of the pediatric population,^{1,2} and the prevalence of CMA has increased in recent years.³ Although the natural history of CMA is generally favorable, previous studies have reported widely varying results as to the pace of clinical recovery.^{4–7} The elimination diet usually prescribed for children with CMA can be associated with potential disadvantages, including malnutrition and psychological problems.^{8,9} Moreover, accidental exposure to CM protein (CMP) is not uncommon because CM is such a common contaminant in food.^{10–12} For these reasons, the possibility of obtaining CM tolerance through oral desensitization has been investigated in children with CMA. Desensitization to CM through immunotherapy has been associated

with a decrease in CM-specific IgE levels.^{13–15} In particular, CM-specific IgG4 levels always have been shown to increase in successful specific oral immunotherapy,^{16–18} suggesting that upregulation of allergen-specific IgG4 responses may be an important event in CM-specific immunotherapy. However, because all these interventions have been performed in children older than 1 year, little is known about the efficacy of oral desensitization and accompanying changes in CM-specific IgE and IgG4 during infancy, when the symptoms of CMA usually start.

This study explored whether a CMP-specific IgG4 response is established at 7 to 12 months of age. In addition, oral desensitization was performed in 7- to 12-month-old infants with CMA to explore whether regular CM exposure in these infants might be efficacious for inducing the CMP-specific IgG4 response accompanying the alleviation of CMA symptoms.

Methods

Patients and Study Design

Initially, 542 patients younger than 16 years who visited the Department of Pediatrics, Chungbuk National University Hospital

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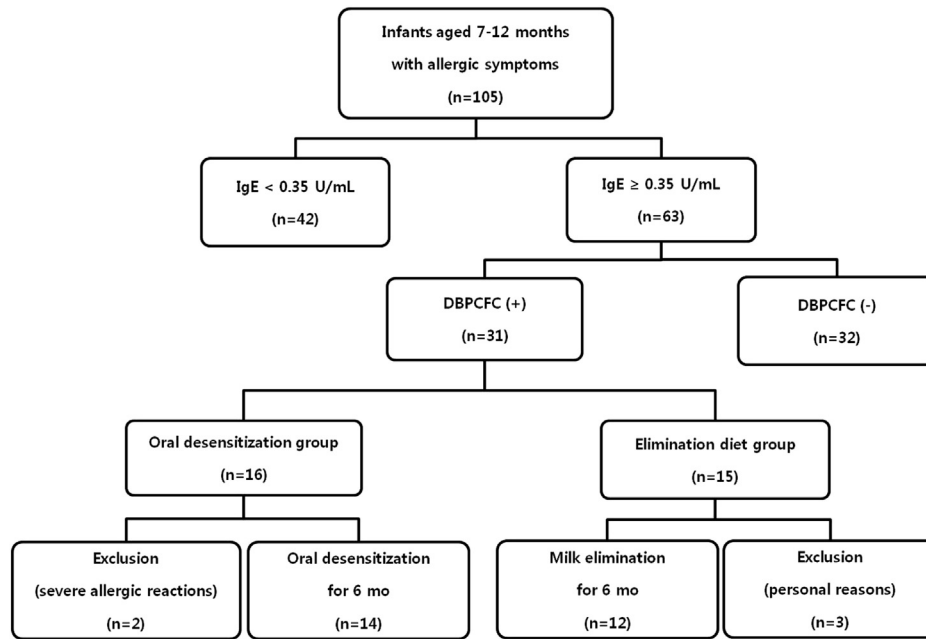


Figure 1. Trial profile showing patient populations analyzed for the efficacy of oral sensitization. DBPCFC, double-blinded, placebo-controlled food challenge.

(Cheongju, Korea) with atopic dermatitis or urticaria/angioedema were enrolled. The levels of CM-specific IgE and specific IgG4 to CMP, including α -lactalbumin, β -lactoglobulin, and casein, were measured in these children using the CAP system (Pharmacia and Upjohn AB Diagnostics, Uppsala, Sweden). Of these children, 262 (mean age 30.9 months, 119 boys) with CM-specific IgE levels higher than 0.35 kU/L were included for the analysis of age-related differences in CM-specific IgE and CMP-specific IgG4 levels. In addition, 7- to 12-month-old CM-sensitized infants were selected and these infants formed 2 groups according to the presence of

CMA to compare CM-specific IgE and CMP-specific IgG4 levels between these groups. Levels of these antibodies in the 2 groups were compared with those in non-CM-sensitized 7- to 12-month-old infants who had no previous CM-related symptoms.

Thirty-one infants 7 to 12 months old were selected based on a history of CMA and a positive reaction to a double-blinded, placebo-controlled food challenge (DBPCFC) for CM. These infants were randomly assigned to oral desensitization ($n = 16$) or an elimination diet ($n = 15$; Fig 1). During the 6-month study period, participants in the elimination diet group were kept on a CM-free diet, whereas those in the oral desensitization group were regularly exposed to CM with dose increments. All participants received food and formulas based on their tolerability.

The oral desensitization dose schedule is presented in Table 1. Because all participants did not have significant symptoms to 0.5 mL of CM during the DBPCFC, a dose escalation was initiated at 0.5 mL. The initial build-up phase took place in the hospital, with a rapid increase in CM dosage every 30 minutes to a maximum of 2 mL. Thereafter, participants began home dosing with 2 mL of CM. Doses were increased every week or decreased based on the frequency and severity of adverse reactions. Families connected to the 2 groups were contacted by regular clinic visits and instructed to phone the study physicians in the event of any adverse reactions. After 6 months, the levels of CM-specific IgE and CMP-specific IgG4 were measured in all

Table 1
Oral desensitization schedule

	CM (mL)	CM protein (mg)
Build-up phase	0.5	16.7
	0.75	25.0
	1	33.3
	1.5	50.0
	2	66.7
Home dosing	2	66.7
	3	100.0
	4	133.3
	5	166.7
	6	200.0
	7	233.3
	8	266.7
	9	300.0
	10	333.3
	12	400.0
	14	466.7
	16	533.3
	18	600.0
	20	666.7
	23	766.7
	26	866.7
	30	1,000.0
	35	1,166.7
	40	1,333.3
	50	1,666.7
	100	3,333.3
	200	6,666.6

Abbreviation: CM, cow's milk.

Table 2
Demographic characteristics of CM-sensitized children who were evaluated for age-related differences in CM-specific IgE and CMP-specific IgG4

Boys/girls, n	119/143
Age (mo), n (%)	
≤6	22 (8.4)
7–12	63 (24.0)
13–24	59 (22.5)
25–36	54 (20.6)
≥37	64 (24.4)
Clinical presentation, n (%)	
Atopic dermatitis	191 (72.9)
Urticaria/angioedema	71 (17.1)

Abbreviations: CM, cow's milk; CMP, cow's milk protein.

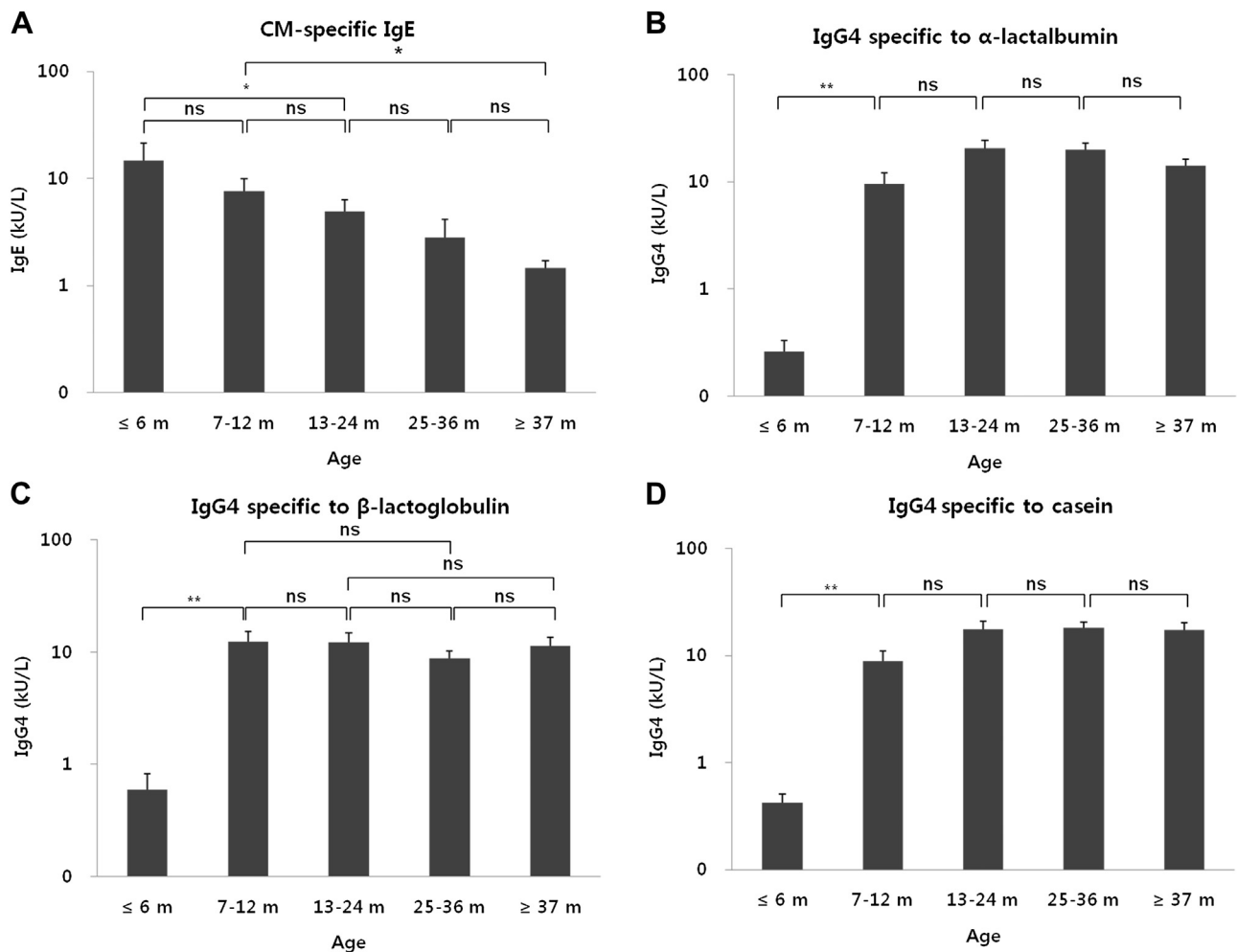


Figure 2. Age-related differences in levels of cow's milk (CM)-specific IgE and IgG4. (A) CM-specific IgE. (B) IgG4 specific to α -lactalbumin. (C) IgG4 specific to β -lactoglobulin. (D) IgG4 specific to casein. * $P < .05$; ** $P < .01$. ns, not significant.

participants to evaluate changes from baseline. Participants under the elimination diet received follow-up DBPCFC. The ethics committee of the Chungbuk National University Hospital institutional review board approved the study and written informed consents were obtained from the parents of all participants.

Double-Blinded, Placebo-Controlled Food Challenge

Of the initially enrolled 105 infants at 7 to 12 months of age, 63 with CM-specific IgE levels higher than 0.35 kU/L were hospitalized and underwent a DBPCFC under the observation of medical personnel. Emergency medications, including diphenhydramine and epinephrine, were prepared at the bedside at all times. The DBPCFC was started with a first dose of 0.1 mL of CM in an amino acid-based infant formula (Neocate; SHS International, Liverpool, United Kingdom) containing vanilla flavoring and sugar. After the initial dose, the participants received increasing doses of 0.5, 1.0, 2.0, 5.0, and 10.0 mL of CM every 30 minutes. The placebo was the amino acid-based infant formula alone with the same vanilla flavoring and sugar. All doses were prepared by clinical research-registered dietitians. After each dose, the participants underwent measurements of vital signs and a physical examination. Food challenges were stopped when adverse reactions appeared or when the maximum tolerated dose of 10.0 mL of CM was reached. All participants were observed for 24 hours after the food challenge.

Statistical Analysis

Statistical analyses were performed using a commercially available software program (SPSS 14.0 for Windows; SPSS, Inc, Chicago, Illinois). Categorical data are presented as numbers and percentages and continuous data as means with standard deviations. For demographic characteristics, the χ^2 test or the Fisher exact test was used for categorical data and the Mann-Whitney test was used for continuous data. The Kruskal-Wallis test was used to compare CM-specific IgE and CMP-specific IgG4 levels between groups. Paired t test was used for the comparison of IgE and IgG4 levels from baseline and month 6. A P value less than .05 was considered significant for all comparisons.

Results

Age-Related Differences of CM-Specific IgE and CMP-Specific IgG4 Levels in CM-Sensitized Children

Two hundred sixty-two children with CM-specific IgE levels higher than 0.35 kU/L were assigned to 1 of 5 groups according to age to observe age-related differences in CM-specific IgE and CMP-specific IgG4 levels (Table 2). CM-specific IgE levels were highest in infants younger than 6 months, and there was a trend that older children had lower levels of CM-specific IgE levels. In contrast, infants younger than 6 months had the lowest CMP-specific IgG4 levels, which were 36.7-, 21.0-, and 21.0-fold lower than in 7- to

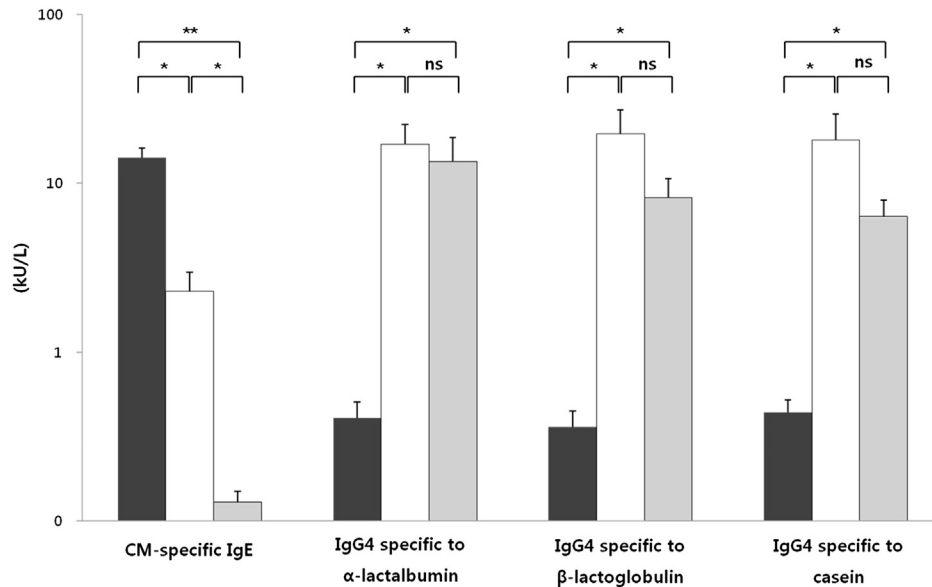


Figure 3. Comparison of cow's milk (CM)-specific IgE and CM protein-specific IgG4 levels in 3 different groups of 7- to 12-month-old infants. Each group was comprised of infants with CM allergy (n = 28) (black bars), CM-sensitized infants without CM allergy (n = 35) (white bars), or non-CM-sensitized infants (n = 35) (gray bars). * $P < .05$; ** $P < .01$. ns, not significant.

12-month-old infants for levels of IgG4 specific for α -lactalbumin ($P = .001$), β -lactoglobulin ($P = .001$), and casein ($P < .001$), respectively (Fig 2). Although α -lactalbumin-specific and casein-specific IgG4 levels in the 7- to 12-month-old infants were lower than those in children older than 12 months, these differences did not reach statistical significance. In addition, β -lactoglobulin-specific IgG4 levels in 7- to 12-month-old infants were similar to those in children older than 12 months. In children older than 12 months, there was no age-related difference in CMP-specific IgG4 levels.

CM-Specific IgE and CMP-Specific IgG4 Levels in 7- to 12-Month Old Infants with and without CMA

Based on the previous dietary history and DBPCFC results, CMA could be defined in 31 of 63 CM-sensitized infants at 7 to 12 months of age. To explore the association of CM-specific IgE and CMP-specific IgG4 levels with the presence of CMA, the difference in the levels of these antibodies was compared between groups with and without CMA. In addition, CM-specific IgE and CMP-specific IgG4 levels were determined in a group of age-matched control infants. CM-specific IgE levels were highest in the CMA group among the 3 groups ($P < .01$; Fig 3). In contrast, CMP-specific IgG4 levels in the CMA group were significantly lower than those in the other groups ($P < .05$). Although CM-specific IgE levels were significantly higher in CM-sensitized infants without CMA than in the controls, there were no significant differences in CMP-specific IgG4 levels between these 2 groups.

Improvement of CMA Symptoms after Oral Desensitization and Elimination Diet

Two infants presented significant adverse reactions during the initial build-up phase, which resulted in their early withdrawal from the oral desensitization protocol. Three patients in the elimination diet group withdrew consent for personal reasons during the period of study. Thus, the full analysis set used for the efficacy analyses included 14 patients in the oral desensitization group and 12 patients in the elimination diet group. The characteristics of the study population are presented in Table 3. No statistically significant differences were noted between the 2 groups based on sex, age, presence of breastfeeding, history of maternal allergy, history

of other food allergy, symptom severity based on the classification by Clark and Ewan,¹⁹ and DBPCFC outcome.

After 6 months, all 14 patients in the oral desensitization group achieved a daily intake of CM equal to at least 200 mL, enough to permit unrestricted CM consumption. In contrast, all 12 patients in the elimination diet group exhibited positivity at follow-up DBPCFC. Although 4 of these patients presented with symptoms to the higher dose than at the previous DBPCFC, less than 10 mL of CM could provoke objective symptoms in all these patients.

Adverse reactions were common in participants in the oral desensitization group. During the desensitization period, 12 of 14 patients (85.7%) presented symptoms with at least 1 dose. These symptoms never occurred after the participants reached 50 mL of CM. All symptoms were mild and local reactions, mainly in the form of immediate urticaria rash around the mouth, increased pruritus, or single wheals. No patient developed severe or unexpected symptoms, including gastrointestinal symptoms or anaphylactic reactions. Allergic symptoms easily resolved without treatment or

Table 3

Baseline characteristics of infants who participated in the study evaluating the efficacy of oral desensitization

Demographic characteristics	Oral desensitization group (n = 14)	Elimination diet group (n = 12)	P value
Boys/girls, n	8/6	5/7	.464
Age (mo), mean $\pm$ SD	8.6 $\pm$ 2.0	8.8 $\pm$ 2.2	.790
Breastfeeding, ^a n (%)	8 (57.1)	7 (58.3)	.717
Maternal history of allergy, n (%)	5 (35.7)	6 (50.0)	.712
Other food allergy, ^b n (%)	9 (64.3)	10 (83.3)	.699
DBPCFC (threshold of reactivity)			
<5.0 mL	3	4	.665
$\geq$ 5.0 mL	11	8	
Severity of CM-related symptoms ^c			
Grade 1	7	8	.635
Grade 2	5	3	
Grade 4	2	1	

Abbreviations: CM, cow's milk; DBPCFC, double-blinded, placebo-controlled food challenge; SD, standard deviation.

^aAt least once per day for 3 months.

^bEgg, soy, peanut, or wheat.

^cSeverity grading of reactions according to Clark and Ewan.¹⁹

Table 4

Changes of CM-specific IgE and CMP-specific IgG4 levels (kU/L) in children receiving oral desensitization and elimination diet

Group	Baseline, ^a mean $\pm$ SD	After 6 mo, mean $\pm$ SD	P value
Oral desensitization group (n = 14)			
CM-specific IgE	16.8 $\pm$ 12.1	6.8 $\pm$ 5.7	.006
Specific IgG4 to α -lactalbumin	0.5 $\pm$ 0.4	21.7 $\pm$ 25.3	.008
Specific IgG4 to β -lactoglobulin	0.4 $\pm$ 0.3	17.2 $\pm$ 20.4	.008
Specific IgG4 to casein	0.5 $\pm$ 0.5	12.8 $\pm$ 10.7	.001
Elimination diet group (n = 12)			
CM-specific IgE	17.3 $\pm$ 13.4	22.1 $\pm$ 24.3	.268
Specific IgG4 to α -lactalbumin	0.3 $\pm$ 0.2	0.7 $\pm$ 1.7	.307
Specific IgG4 to β -lactoglobulin	0.3 $\pm$ 0.5	0.5 $\pm$ 0.4	.128
Specific IgG4 to casein	0.4 $\pm$ 0.3	0.6 $\pm$ 0.4	.072

Abbreviations: CM, cow's milk; SD, standard deviation.

^aNo statistically significant differences in CM-specific IgE and cow's milk protein-specific IgG4 levels between the oral desensitization and elimination diet groups.

after the use of antihistamine, although the length of the desensitization process was increased. In the elimination diet group, 3 of 12 patients (25.0%) had mild adverse reactions, probably caused by accidental exposure to CM during the study period, and easily recovered without treatment or after the use of oral antihistamine.

At baseline, there were no differences in CM-specific IgE and CMP-specific IgG4 levels between the 2 groups (Table 4). In the oral desensitization group, CM-specific IgE levels were significantly lower than at baseline, whereas CMP-specific IgG4 levels were significantly increased ($P < .01$). In contrast, CM-specific IgE and CMP-specific IgG4 levels remained unchanged in patients in the elimination diet group.

Discussion

Despite the mixed results for the chance of recovery from CMA during childhood, it is quite likely that a substantial proportion of children become tolerant to CM as they grow older. This age-related recovery has been reported to be accompanied by the decrease of CM-specific IgE levels.^{6,20,21} Thus, the higher CM-specific IgE levels in the younger groups in the present study appear to be well matched with an age-related recovery from CMA. In contrast, CMP-specific IgG4 levels were lowest in infants younger than 6 months. In particular, the CMP-specific IgG4 levels in these infants were lower than those in infants at 7 to 12 months of age, whose CMP-specific IgG4 levels were comparable to those in the older groups. These findings imply that children at 7 to 12 months of age can develop a sufficient CMP-specific IgG4 response.

However, the CMP-specific IgG4 responses were not sufficiently developed in 7- to 12-month-old infants with CMA because these infants had significantly lower CMP-specific IgG4 levels than the age-matched controls without CMA. Thus, lower levels of the CMP-specific IgG4 in 7- to 12-month-old infants with CMA suggest that measurement of CMP-specific IgG4 levels can assist in assessing the achievement of tolerance to CM during infancy. Lower levels of CMP-specific IgG4 in 7- to 12-month-old children with CMA may be explained by the lower levels of exposure to CM. Regular exposure to CMP had been withheld in these infants because their parents noticed repeated reactions after introducing CM. Therefore, deprivation of exposure to CMP might result in the delay of the CMP-specific IgG4 response in infants with CMA.

The elimination of CM represents the mainstay of treatment in preventing further reactions in most children affected by CMA. However, strict avoidance of CM is often an unrealistic therapeutic approach, because CM might represent an essential component of the diet during childhood. Therefore, desensitization induction can be considered for children with CMA as a management strategy. In particular, oral desensitization for children with a milder form of CMA

can be performed with less danger of severe reactions. Thus, more aggressive intervention with oral desensitization may be appropriate for these children to avoid the nutritional problems that are important issues for their parents. Because the present study population was on average less severely allergic, the risk of reactions in most infants receiving oral desensitization was within the acceptable range, as expected. Reactions in these infants ranged from erythematous rashes to single wheals and resolved spontaneously or with oral antihistamines. In addition, smaller dose increments in this study might have lessened the reaction frequency or severity. During the course of the study, the level of parents' motivations for their child to receive oral desensitization was high because they were aware of CMA-related problems and of discomfort from CM avoidance. For these reasons, parents chose to continue the administration of CM despite symptoms during oral desensitization.

Patients included in all previous investigations on the efficacy of oral desensitization were older than 1 year.^{14–17} However, an earlier intervention would be better for children with CMA because alternative therapies to elimination diets need to be performed as soon as possible. In fact, few conclusions about infant feeding to prevent allergic disease can be reached from the currently available data. No population study to date has directly examined the relation between infant feeding in the first year of life and risk of confirmed infant food allergy. Thus far, studies eliminating food allergens during infancy have consistently failed to prevent IgE-mediated food allergy.^{22–24} Instead, in a large observational cohort of children, Poole et al²⁵ found that delaying the initial exposure to cereal grains might increase the risk of IgE-mediated wheat allergy. In addition, Du Toit et al²⁶ found a strong inverse association between peanut consumption in infancy and the prevalence of peanut allergy in childhood. These findings imply the requirement of early oral exposure for tolerance induction and provide the evidence base for a benefit of an early CM introduction for infants with CMA in the present study.

In this study, 87.5% of infants (14 of 16) receiving oral desensitization were able to ingest CM after 6 months without any restrictions, whereas 2 infants in the same group had to withdraw from the schedule owing to significant adverse reactions. In contrast, all infants receiving the elimination diet had a positive food challenge reaction. The efficacy rate for oral desensitization in the present study is comparable to those in previous reports.^{14,27,28} However, because all successfully desensitized infants continued to consume CM daily, it is not clear whether they were fully tolerant or transiently desensitized and thus still at risk of future reactions. No infant receiving the elimination diet spontaneously acquired tolerance after 6 months of observation, although this period was not long enough to raise the possibility that the elimination diet might be associated with a lower chance of spontaneous tolerance.

In the oral desensitization group, CM-specific IgE antibody levels were found to decrease after 6 months, whereas CMP-specific IgG4 antibody levels exhibited a large increase at the same time point. These changes were not observed in infants who were deprived of regular CM exposure. Thus, these findings support the notion that regular food exposure with dose increments results in immunologic changes leading to a dampened allergic response. This finding is in line with several previous observations on levels of antigen-specific IgE and IgG4 in desensitization to food allergens.^{28–30} In particular, increases of allergen-specific IgG4 levels have always been consistent findings even in previous immunotherapies that were not associated with a decrease in food-specific IgE levels.^{17,31,32} In addition, IgG4 binding to CM epitopes has been reported to increase over time in patients who recovered from CMA compared with children who remained allergic to CMP,³³ suggesting the role of IgG4 in the development of tolerance. However, the role of IgG4 in tolerance development remained controversial because there was no relation between allergen-specific IgG4 levels and a natural

development of tolerance.^{34,35} Furthermore, there was no apparent association between the degree of increase in CM-specific IgG4 level and the observed clinical outcome in a previous study evaluating the efficacy of oral desensitization.¹⁷ Therefore, whether the upregulation of an allergen-specific IgG4 response is a critical mechanism for the alleviation of CMA symptoms or a mere indication of repeated CM exposure warrants further investigations.

One limitation of this study is that the effectiveness of CM desensitization was not evaluated in a double-blinded fashion. Thus, the authors cannot rule out spontaneous desensitization in the infants who underwent oral desensitization. However, our findings support the effectiveness of earlier intervention with CM exposure for the alleviation of CMA symptoms, which was not achieved with the elimination diet. Another limitation is that the study population in this study had relatively mild to moderate CMA as reflected by the relatively low levels of CM-specific IgE and low-grade CM-related reactions in these patients. Thus, the pattern of response in infants with severe CMA could not be presented in this study, and further investigation for data on patients with severe CMA should be required.

In summary, CMP-specific IgG4 responses did not develop sufficiently in 7- to 12-month-old infants with CMA, whereas these responses were established in age-matched infants without CMA. In addition, regular CM exposure with dose increments in 7- to 12-month-old infants with CMA was associated with the upregulation of CMP-specific IgG4 responses accompanying CM desensitization. Thus, these findings support active therapy with regular exposure to the allergen instead of strict avoidance as a strategy for treating infants with CMA.

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