

Soy allergy in infants and children with IgE-associated cow's milk allergy

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Objectives: To determine the prevalence of soy allergy in IgE-associated cow's milk allergy (CMA).

Study design: Children <3.5 years with documented IgE-associated CMA (n = 93) were evaluated for soy allergy by double-blind, placebo-controlled food challenge, open challenge, or convincing previous history of an anaphylactic reaction to soy. Children tolerant to soy at entry received soy formula and were followed up for 1 year.

Results: Of this IgE-associated CMA cohort (ages 3 to 41 months), 14% (95% CI = 7.7%-22.7%) were determined to have soy allergy, 12 definitely at entry and 1 possibly after 1 year of soy ingestion. The latter child experienced severe failure to thrive at enrollment and exhibited improved growth while receiving soy during follow-up but was diagnosed with eosinophilic esophagitis at study completion. Improved growth ($P < .05$) occurred in the non-soy-allergic cohort ingesting soy formula (579 ± 31 mL/d) during the year of follow-up.

Conclusions: Soy allergy occurs in only a small minority of young children with IgE-associated CMA. As such, soy formula may provide a safe and growth-promoting alternative for the majority of children with IgE-associated CMA shown to be soy tolerant at the time of introduction of soy formula. (J Pediatr 1999;134:614-22)

cally within 3 hours of CM challenge in individuals with demonstrable specific CM-IgE.⁴ CMA not associated with CM-IgE is represented by CM-induced enterocolitis/enteropathy syndromes manifested predominantly by gastrointestinal symptoms.¹⁻⁵

CM	Cow's milk
CMA	Cow's milk allergy
DBPCFC	Double-blind, placebo-controlled food challenge
EPH	Extensively hydrolyzed protein hydrolysate
NCHS	National Center for Health Statistics
SPT	Skin prick test

The prevalence of concomitant soy intolerance in CMA has ranged between 0% and 63%,^{2,5-25} with higher levels generally reported in non-IgE-associated enterocolitis/enteropathy syndromes.²⁶ The true prevalence of soy allergy in documented IgE-associated CMA is unknown. For this reason, some CM-sensitive infants are being switched to an extensively hydrolyzed protein hydrolysate formula to avoid the potential sensitization to soy proteins. These EPH formulas may be less palatable and cost at least twice as much as soy formula.²⁶ As such, it is important to determine the prevalence of soy allergy in young children with IgE-associated CMA. This study demonstrates that concomitant soy allergy occurs in <15% of infants and toddlers with IgE-associated CMA, indicating that soy feeding may be a safe alternative for the majority of children with IgE-associated CMA who do not have clinical symptoms in response to soy.

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Cow's milk allergy affects about 2.5% of children <3 years of age.^{1,2} Various signs and symptoms have been associated with cow's milk protein sensitivity, including gastrointestinal, dermatologic, and respiratory/circulatory events.³ These reactions may be immediate or occur >24 hours after exposure to CM and may or may not be associated with gastrointestinal mucosal damage. CMA has been classified immunologically into IgE-associated and non-IgE-associated reactions, with some conditions such as eosinophilic gastroenteropathies evidencing overlap.³ IgE-associated CMA manifests symptoms typi-

METHODS

Cohort

Children <3.5 years of age who met the criteria for diagnosis of IgE-associated CMA were enrolled in this multicenter study. Their parents were informed about the study on their initial visit during which they read and signed an informed consent form approved by the institutional review board from each center.

Study Design

After a detailed medical history and results of physical examination were obtained, the patients underwent skin prick tests with CM and soy, followed by food challenges. Children without a convincing recent history of a significant adverse reaction to CM or soy underwent double-blind, placebo-controlled food challenge with CM and/or soy. Those with negative DBPCFC responses to CM were not entered into the trial. Children with a positive DBPCFC challenge response to soy were determined to have soy allergy as defined above. Children with negative DBPCFC responses and negative open soy challenge responses were offered soy formula as a beverage at home for 12 months. It was recommended that children consume a minimum of 6 to 8 fl oz of soy formula per day. Children without soy allergy at entry were followed up with visits at 2 months and 1 year after entry to determine dietary intake, tolerance to soy formula, and anthropometric data. Dietary intake was assessed for 3 days before each follow-up visit. A 6-month telephone contact was made to assess tolerance to the soy formula, at which time parents completed dietary intake and tolerance surveys.

Diagnosis of CMA and Soy Allergy

IgE-associated CMA was established by a history of "immediate" reaction (within 4 hours) to CM protein, a positive SPT response to CM or CM-IgE, and a positive DBPCFC ($n = 56$) or

open challenge ($n = 1$) response to CM or history of more than one immediate anaphylactic reaction to an isolated ingestion of CM, the last being within 5 months of entry into the study ($n = 33$), or if >5 months, demonstration of CM-IgE >20 U/mL ($n = 3$).^{28,29} Soy allergy was established by a positive DBPCFC response to soy, convincing open challenge response under the direction of a physician, or history of more than one immediate anaphylactic reaction to an isolated ingestion of soy.

Food Challenges

Separate food challenge randomization schedules were prepared for each study site. Previously described food challenge procedures were followed³⁰ and are only summarized here. Testing was done over a 3-day period. Two DBPCFCs were done on the first 2 days. One DBPCFC consisted of the administration of either CM or soy (Isomil Soy Formula with Iron; Ross Products Division, Abbott Laboratories) or placebo in the morning and afternoon during 1 day, followed on the next day with the other food or placebo. The active foods contained either 10 g of non-fat dry milk or Isomil Powder dissolved in approximately 100 mL of Alimument Protein Hydrolysate Formula with Iron RTF (Ross Products Division, Abbott Laboratories). Placebo consisted of 100 mL of Alimument. The sequence of foods used in the oral challenges was determined by a computerized randomization program. The dietetic staff or a designated nurse not involved in the challenge studies prepared the test foods so that their identity was hidden to children, parents, physicians, and nurses administering the oral challenges. For children undergoing only soy challenges, a negative DBPCFC response to soy or placebo was followed on the next day with an open soy challenge. Children avoided antihistamines for 5 to 7 days and β -agonists for 12 hours before food challenges. Food challenges were administered in 6 to 7 doubling doses (starting

at 1 drop to 5 mL, depending on child's suspected clinical sensitivity) and given at 10- to 15-minute intervals; the 100 mL challenge, if tolerated, was usually completed in approximately 1 hour. A physician confirmed all reactions, which were recorded by the nursing staff on a standardized symptom sheet that noted the type, time of onset, severity, and duration of the reaction.³¹ Emergency drugs and equipment were available to treat adverse reactions. The randomized sequence code was broken after the completion of the 2-day DBPCFC procedures. On the day after the completion of the double-blind challenges, 4 to 6 fl oz of Isomil (20 cal/fl oz) was fed openly to assure that the formula was tolerated without symptoms. Additional DBPCFCs with soy were performed in children whose parents reported symptoms possibly related to soy during the course of the 1-year follow-up.

Skin Tests and Total and Specific IgE

Skin tests were performed on all patients before the food challenges with CM and soy, and in some centers, with other foods suspected of causing symptoms by the SPT technique. The food allergens were glycerinated extracts at a 1:20 (wt/vol) concentration (Greer Laboratories, Lenoir, NC). A cellophane tape record of the SPT results was kept for each patient. Wheal reactions 3 mm greater than the control reaction (glycerinated saline) were considered positive.³² Blood samples were obtained for determination of total IgE by PRIST (Pharmacia Diagnostics AB, Uppsala, Sweden) and for CM and soy-specific IgE by FEIA CAP (Pharmacia Diagnostics AB). Serum from one center was inadvertently lost during shipment to the evaluating center, precluding determination of total and specific IgE levels in those children.

Anthropometric Data

Weight, length, and head circumference data were obtained in a standard-

Table I. Demographic and anthropometric characteristics of CMA cohort (n = 93)

Parameter	Mean (SEM) or % (values based on n = 93 unless noted)
Demographic	
Age at enrollment	19.1 (0.9)
≤6 mo	3.2%
>6 to 12 mo	17.2%
>12 to 24 mo	54.8%
>24 to 36 mo	20.4%
>36 to 42 mo	4.3%
Gender (% male)	72.0%
Ethnicity	
Caucasian	84.9%
African-American	5.4%
Hispanic	3.2%
Other	6.5%
Atopic dermatitis and/or asthma	65.6%
Anthropometric	
Birth weight (kg)	3.5 (0.1) (n = 92)
Birth length (cm)	51.2 (0.5) (n = 82)
Weight at entry (NCHS z-score)	-0.32 (0.1) (n = 91)
Height at entry (NCHS z-score)	-0.18 (0.1)
Weight for length at entry (NCHS z-score)	-0.22 (0.1) (n = 91)
Head circumference at entry (NCHS z-score)	0.19 (0.1) (n = 73)

ized manner. For weight, the scale was calibrated weekly and infants were weighed nude; 2 measurements were obtained and were only accepted if the 2 measurements were within 10 g or ½ oz. Lengths were measured to the nearest 0.1 cm on a recumbent length board for infants and a stadiometer for older children. Two measurements needed to be within 0.2 cm to be accepted. Similac INSER-TAPE was used to measure head circumference to the nearest 0.1 cm; 2 measurements were accepted if within 0.2 cm. Growth parameters are reported with National Center for Health Statistics z-scores.

Data Analysis

The primary outcome was the prevalence of soy allergy in subjects with IgE-associated CMA as determined by DBPCFC or convincing history of anaphylaxis in response to soy formula. The prevalence and 95% confidence limits of soy allergy were determined

by Exact Confidence Limits. Analyses used the 2-sided *t* test for continuous variables and χ^2 or Fisher's exact test for categorical variables. To test whether there was a trend in time in anthropometric z-scores over the year of follow-up during soy formula feeding of subjects not allergic to soy at entry who had data for all time points, a growth modeling approach was used. A linear regression line was fitted to each subject's growth over time, and then a *t* test was used to determine whether the difference in the slopes was significantly different from zero. Significance was set at $P \leq .05$.

RESULTS

Cohort Characteristics

The demographic/anthropometric and immunologic characteristics of the 93 children in this cohort with IgE-associated CMA are highlighted in Tables I and II, respectively. IgE-associated CMA started at 5.6 months of age and

existed for 13.4 months by the time of enrollment (Table I). The feeding routine of the cohort before enrollment included breast milk (n = 6), soy formula (n = 63), EPH (n = 20), amino acid-based formula (n = 2), and other (n = 2). Of the cohort, 88% had been exposed to soy formula before enrollment; 24% demonstrated a positive SPT response to soy and 59% had soy-IgE (Table II). Of 26 children re-challenged with CM at the completion of the study, 35% had negative CM challenge responses.

The cohort at Johns Hopkins (n = 48), a tertiary referral center for multiple food hypersensitivity, compared with the other 3 centers (n = 45), was older at entry (22.1 ± 1.0 months vs 15.9 ± 1.2 months, $P < .001$) and had CMA of longer duration (15.1 ± 1.2 months vs 11.5 ± 1.2 months, $P < .05$). The characteristics of the subjects in the 4 centers were otherwise demographically, immunologically, and anthropometrically comparable (data not shown).

Identification and Development of Soy Allergy

At entry, soy allergy was definitely diagnosed in 13% (n = 12) of the cohort documented by DBPCFC (n = 8), open challenge (n = 2), or convincing history of anaphylaxis and a high level of soy-IgE (≥ 10 U/mL) (n = 2) (Table III).

Subjects without soy allergy at entry (n = 81) were then followed up for 1 year on a feeding regimen that excluded all CM products and recommended soy formula feeding. A mean daily amount of 578.6 ± 30.6 mL (range, 39 to 1165 mL) (n = 78) soy formula was ingested by these children during the year of follow-up. Three parents removed their children from the study at 2, 6, and 7 months because the children refused soy formula when weaned from bottle to cup feeding; these children did not have symptoms in response to the soy formula during the time of consumption nor to soy-containing foods after discontinuation of the formula.

Two children with reported symptoms possibly related to soy during follow-up tolerated soy on repeat DBPCFC and continued to receive soy formula.

One child (A6), who had very severe failure to thrive (NCHS z-scores for weight and height of -2.99 and -2.41 , respectively) before enrollment and a history of soy intolerance at age 5 months but negative DBPCFC and open soy challenge responses at entry, consumed about 30 fl oz of soy formula daily during the study. At study completion this child had improved z-scores for weight ($+0.64$ units) and height ($+0.78$ units) but had biopsy-proven eosinophilic esophagitis and was switched to an amino acid-based formula. Though there was an intermittent history of vomiting and nasal symptoms with soy feeding at study completion, a DBPCFC with soy could not be done to prove the association. It is probable that this child had soy-induced enterocolitis at the onset of the study, but the soy challenge at entry was not sensitive enough to diagnose the condition at that time.

When the definitive diagnoses of soy allergy at entry ($n = 12$) and the possible diagnosis at exit ($n = 1$) were combined, this IgE-associated CMA cohort had a maximum concomitant soy allergy prevalence of 14.0% (95% CI = 7.7%-22.7%). All but one of the children with soy allergy demonstrated a soy positive SPT response and/or soy-IgE. A non-IgE association was seen in one child (A11) who had biopsy-diagnosed eosinophilic esophagitis (Table III).

Children with soy allergy ($n = 13$) compared with those without soy allergy ($n = 80$) were older (23.4 ± 2.5 vs 18.4 ± 0.9 months, $P < .05$), exhibited lower height z-scores (-0.73 ± 0.26 vs -0.09 ± 0.12 , $P < .05$), had a higher prevalence of positive soy SPT responses (69.2% vs 16.7% [$n = 78$], $P < .0002$), and showed higher levels of soy-IgE (13.0 ± 5.6 vs 3.4 ± 1.1 U/mL [$n = 51$], $P < .01$). Children with soy allergy compared with those who were soy-tolerant exhibited a higher preva-

Table II. Immunologic characteristics of CMA cohort ($n = 93$)

Parameter	Mean (SEM) and range or % (values based on $n = 93$ unless noted)
CMA	
Onset of CMA (mo)	5.6 (0.5)
Duration of CMA (mo)	13.4 (0.9)
Positive CM SPT and/or ELISA results (%)	100
Diagnosis	
Positive CM challenge	
DBPCFC (%)	60.2
Open challenge (%)	1.1
Total positive challenges (%)	61.3
CM triggering reaction (mL)	24.5(4.9) (0.1-167) ($n = 57$)
Time to reaction (min)	29.1(6.9) (1.0-390) ($n = 57$)
Epinephrine required (%)	7.5 ($n = 57$)
Convincing history at enrollment	
Anaphylactic and/or multisystem (%)	31.2
Single system (%)	7.5
Total (%)	38.7
Symptoms	
Anaphylactic (%)	33.3
Gastrointestinal (%)	52.7
Respiratory (%)	57.0
Dermal (%)	93.5
Multisystem (%)	77.4
Allergy evaluation	
Serum IgE level (IU/mL)	487 (109) ($n = 37$)
Positive SPT response to CM (%)	98.9 ($n = 89$)
Positive CM-IgE (%)	93.8 ($n = 64$)
Serum CM-IgE (U/mL)	25.4 (3.8) ($n = 64$)
Positive SPT response to soy (%)	24.2 ($n = 91$)
Positive soy-IgE (%)	59.4 ($n = 64$)
Serum soy-IgE (U/mL)	5.3 (1.5) ($n = 64$)

ELISA, Enzyme-linked immunosorbent assay.

lence of history of EPH intolerance (30.8% vs 8.8%, $P < .05$).

A positive soy SPT response was only partially predictive of soy allergy ($P = .0002$), exhibiting the following statistical capacities to predict soy allergy in this CMA cohort: 69.2% sensitivity (9/13), 83.3% specificity (65/78), 40.9% positive predictive value (9/22), 94.2% negative predictive value (65/69), and 81.3% efficiency (74/91). Soy-IgE determined by FEIA in only a subgroup of the cohort ($n = 64$) was a poor predictor of soy allergy ($P = .062$), consistent with previous reports.^{29,33-35} Soy allergy occurred almost exclusively and

with a prevalence of 25% (12/48) in subjects from one of the study sites (Johns Hopkins) compared with 2.2% (1/45) of subjects from the other 3 centers ($P = .0018$). The quantity of soy formula ingestion was similar in the patients at all the centers (data not reported, $P < .05$). The prevalence of a positive soy SPT response was also greater in the Johns Hopkins cohort (34.8% [16/46]) than in the other 3 centers (13.3% [6/45]) ($P = .017$).

Other Food Allergies

Multiple food allergies were frequent in this CMA cohort. At least one other

Table III. Characteristics of patients with CMA and documented soy allergy

Patient No.	Age at study start (mo)	Soy allergy onset (mo)	Soy SPT	Soy IgE (U/mL)	Diagnosis of soy allergy (age in mo)	Symptoms	Soy (mL)	Time to reaction (min)	Food allergies in addition to CM and soy	Other illnesses
A6	19	5	+	20	History (see text) (33)	N, FTT, V	NC	NC	Yes	EE, FTT
A7	28	1.5	+	4	+ DBPCSC (28)	D, P, V	38	72	Yes	AD, As, EGE, FTT
A11	30	Infant	—	—	+ Open soy challenge (30)	D, N, V, W	120	300	Yes	Esophagitis, FTT
A23	39	6	+	6	+ DBPCSC (39)	D, P, R, V	60	88	Yes	AD
A24	38	2.5	—	73	+ DBPCSC (38)	C, P, R	60	60	Yes	AD, As
A25	19	1	+	1	+ DBPCSC (19)	P, V	65	50	Yes	AD, GER
A26	22	3	—	16	+ Open soy challenge (22)	P, U, R	60	96	Yes	AD, GER
A27	19	11	+	10	Anaphylaxis (12)	D, N, W	NC	NC	Yes	AD, As, EC
A28	30	6	+	28	Anaphylaxis (6)	U, V	NC	NC	Yes	AD
A29	16	0.5	+	—	+ DBPCSC (15)	N, R, V	40	30	No	FTT, GER
A30	19	0.5	+	2	+ DBPCSC (19)	D, N, U, V	100	180	Yes	FTT, PLE
A37	18	2	—	2	+ DBPCSC (18)	N, U, V	29	20	Yes	None
B16	8	4.5	+	7	+ DBPCSC (12)	N, R	75	115	No	GER

N, Nasal symptoms; *FTT*, failure to thrive; *V*, vomiting; *NC*, not challenged; *EE*, eosinophilic esophagitis; *DBPCSC*, double-blind, placebo-controlled soy challenge; *D*, diarrhea; *P*, pruritis; *AD*, atopic dermatitis; *As*, asthma; *EGE*, eosinophilic gastroenteritis; *W*, wheeze; *R*, rash; *C*, cough; *GER*, gastroesophageal reflux; *U*, urticaria; *EC*, enterocolitis; *PLE*, protein-losing enteropathy.

food allergy in addition to CM was confirmed by challenge or anaphylaxis or was suspected by clinical history in 64.5% of the cohort. A high prevalence of food allergies was observed for egg (39.8%), peanut (21.5%), meat (17.2%), and wheat (16.1%), with 31% confirmed by DBPCFC or anaphylaxis. A wide variety of other foods was associated with food allergies in prevalences <10%, including any fruit, fish, other

grains, legumes, other vegetables, crustacea, and tree nuts.

Before study enrollment, 10.7% ($n = 10$) of the CMA cohort had convincing histories of intolerance to EPHs, 4 confirmed by challenge and one by anaphylaxis; these children were not challenged with Alimentum during this study. One of the 63 (1.6%) children challenged with Alimentum during this study had a positive reaction. It should be noted that intolerance to EPH was

observed almost exclusively at Johns Hopkins (20.8% [10/48]) compared with the other centers (2.2% [1/45]) ($P = .005$).

Growth Parameters

Fitting a linear regression line to each subject's growth over the year of follow-up of children not allergic to soy at entry and ingesting soy formula showed that there was a significant trend for increases in anthropometric

Table IV. Reported soy allergy in CMA

Reference	CMA diagnosis	CMA (n)	CMA immunology	Age (mo) mean/median	Soy diagnosis	Soy allergy in subjects with CMA (%)
7	OC	75	Mixed	NR	History	36
8	OC	50	Mixed	<12	History	20
9	OC	35	Non-IgE	5	OC	11
10	OC	18	Mixed	NR	History	22
6	OC	8	Non-IgE	1	OC	63
2	OC	20	Mixed	6	History	35
12	OC	8	Non-IgE	11	History	25
12	OC	7	IgE	8	History	0
13	OC	103	Non-IgE	NR	OC	11
24	OC	75	Mixed	NR	History	43
14	OC	4	Non-IgE	5	OC	100
15	OC	9	Non-IgE	5	OC	44
17	OC	29	Mixed	NR	OC	17
16	OC or other*	54	Mixed	NR	History	29
20	DBPCFC	54	IgE	NR	History	7
19	OC	20	Mixed (AD only)	6	History	5
18	OC	78	Mixed	16	History	47
21	OC	22	Mixed	29	History	18
22	OC	19	Mixed	11	OC	32
23	DBPCFC	20	IgE	31	OC	0
5	OC	10	Non-IgE	6	OC	60
25	OC	29	Non-IgE	3	History	17
Total combined		749				26
Present cohort	DBPCFC, OC, or ANA	93	IgE	19	DBPCFC, OC, or ANA	14

OC, Open challenge; *Mixed*, both IgE and non-IgE-associated populations; NR, not reported; *Non-IgE*, gastrointestinal disorder only; AD, atopic dermatitis; ANA, anaphylaxis.
*Convincing immediate history plus CM-IgE and clinical remission with CM avoidance.

NCHS z-scores over the year for both height ($n = 74$) (-0.06 ± 0.13 at entry, 0.09 ± 0.12 at 2 to 6 months, and 0.20 ± 0.11 at 7 to 12 months; $P = .0007$) and weight ($n = 73$) (-0.29 ± 0.12 at entry, -0.15 ± 0.13 at 2 to 6 months, and -0.14 ± 0.11 at 7 to 12 months; $P = .03$).

DISCUSSION

The strength of this study to determine the prevalence of soy allergy in IgE-associated CMA lies in (1) its large cohort size, (2) inclusion of only patients with IgE-associated CMA, (3) precise documentation of CMA and

soy allergy, and (4) intensive 1-year prospective follow-up to determine the development of soy allergy. Of the infants and toddlers with IgE-associated CMA in this series, 14% were shown to have soy allergy, with 12 of 13 evidencing it at entry. Possible development of soy allergy occurred in only one child during the 1-year follow-up; this child had the multiple food hypersensitivity syndrome and eosinophilic esophagitis.^{36,37} Soy formula feeding in those not allergic to soy at entry was well tolerated, and significant improvements in NCHS z-scores for weight and height occurred during follow-up.

An attempt was made to identify distinguishing characteristics of patients

in this IgE-associated CMA cohort who had concomitant soy allergy. The most discriminating factor for soy allergy was the presence of a positive SPT response to soy, but the positive predictive value was low (41%), although the negative predictive value was high (94%), consistent with other reports.^{29,35} It should be emphasized that these findings can only be applied to IgE-associated CMA and have no relevance to non-IgE-associated disorders such as food-protein enterocolitis/enteropathy.⁵ The higher prevalence of soy-IgE by FEIA compared with positive soy SPT responses in this highly atopic CMA cohort with multiple food sensitivities may be due to cross-react-

ing antibodies measured in the in vitro assay as suggested previously,¹⁷ a higher affinity soy allergen in the FEIA test, or other unknown reasons.

Previous studies that evaluated concomitant CMA and soy allergy report prevalences ranging as low as 0% and as high as 63% in cohorts of at least 5 (Table IV), with the higher prevalences seen in those children with exclusively gastrointestinal symptoms (enterocolitis and enteropathy). This variability may be due to differences in: (1) the immunologic mechanism associated with CMA in the studied cohort, (2) diagnostic accuracy, (3) cohort size, (4) specialty referral, and (5) unknown factors.³⁸ The finding of a 14% prevalence of soy allergy in IgE-associated CMA is consistent with the prevalence noted in smaller less well documented studies of IgE-associated CMA. It should be observed that only a minority of prior studies diagnosed soy allergy by means of a physician-observed food challenge, and none performed these challenges with DBPCFC methodology (Table IV).

A recruitment bias occurred in this study. Twelve of 13 of the children with soy allergy were enrolled in 1 of the 4 centers, a tertiary specialty referral center for multiple food sensitivities in children. Nevertheless, the large cohort size of this study provides a clinically useful estimate of the concomitant occurrence of soy allergy in young children with IgE-associated CMA.

It would have been preferable to have instituted a birth cohort study to identify both CMA and soy allergy at their time of onset (usually before 6 months of age). To prospectively identify 100 infants with IgE-associated CMA, it would be necessary to recruit a birth cohort of approximately 7000 unselected or 1000 high-risk newborns, given the reported incidence of CMA in an unselected cohort (2.5% with 60% caused by an IgE mechanism)¹ and 10% to 15% in a high-risk cohort.³ Notwithstanding this limitation, this study provides a clinically useful estimate of soy allergy in patients with IgE-associated CMA, but possibly lower than that

obtained had the evaluations been done earlier in infancy.

The treatment for infants with CM protein sensitivity involves removal of cow's milk protein from the diet and feeding with soy, EPH, amino acid-based, or meat-based formulas. Soy protein possesses immunogenicity and allergenicity, albeit less than CM.³⁹⁻⁴¹ In addition, soybean allergens have been partially identified and characterized.⁴²⁻⁴⁴ Several recent prospective studies report extremely low prevalences of soy allergy both in children with food allergy (<5%)⁴⁵⁻⁴⁸ and infants of atopic parents fed soy formula from birth or early in life (0.5%),⁴⁹ although higher prevalences have been reported.²⁷

Previous studies report prevalences of CM intolerance of about 5% with EPH and over 40% with partial protein hydrolysates in IgE-associated CMA.^{3,50,51} Therefore partial protein hydrolysates have no role in the feeding of infants with IgE-associated CMA because of the frequent adverse reactions reported with these products in this atopic condition.^{3,50,51,52} Additionally, a greater prevalence of EPH intolerance occurs in infants and children with the multiple food hypersensitivity syndrome, a group that often only tolerates amino acid-based formula.^{37,53-55} In the cohort in this study, about 30% of those found to be allergic to soy also had a history of intolerance to EPH, many of whom also had features of the multiple food hypersensitivity syndrome.

Implications

The findings of this study suggest that a soy-based formula is generally a safe formula for infants and toddlers with IgE-associated CMA, consistent with recent recommendations of the Committee of Nutrition of the American Academy of Pediatrics.²⁶ Given the lower cost and greater palatability of soy compared with EPH formula^{27,49} and the improved growth in height and weight with 1 year of soy

formula feeding noted in this study, soy formula may be considered a first-choice alternative formula in children with IgE-associated CMA and documented negative soy challenge responses. Soy formula should be introduced under physician observation to document tolerance. Because only 5% of this IgE-associated CMA cohort were <6 months of age at the time of evaluation and challenge, these recommendations may or may not apply to this younger age group. On the other hand, soy formula feeding cannot be routinely recommended in those infants and toddlers with non-IgE-associated CMA (enterocolitis/enteropathy), because previous studies report a very high prevalence of concomitant soy allergy in this nonatopic subset.^{5,26}

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