

Usefulness of a Cow's Milk Whey Infant Formula (Good Start) in the Management of Children with Group 1A (Topical Reactors) IgE-Mediated Cow's Milk Allergy

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ABSTRACT

Despite the fact that cow's milk protein hydrolysate infant formulas have reduced allergenicity (i.e., are hypoallergenic), all of those that are currently commercially available in the United States have caused anaphylactic reactions in highly sensitized children with IgE-mediated cow's milk allergy (CMA). Skin prick testing (SPT) with CM, a whey hydrolysate (Good Start), and a casein hydrolysate (Nutramigen) can identify those children with mild topical IgE-mediated CMA (group 1A) and separate them from those children with more severe systemic IgE-mediated CMA (groups 1B and 1C). Thirteen children in group 1A tolerated a whey hydrolysate formula (Good Start) when challenged with it and when fed the formula daily for at least 2 weeks. All (13/13) were challenge-positive to CM before the Good Start challenge and trial. Eleven (11/13) remained challenge-positive after being fed Good Start. There was no change in their level of sensitivity during the interval. Two children outgrew their clinical sensitivity to CM. Good Start is recommended for children with mild IgE-mediated CMA (Group 1A). In contrast, in a double-blind, placebo-controlled study, we have shown that 62% (8/13) of children with group 1B or 1C IgE-mediated CMA had systemic urticarial and respiratory reactions when fed Good Start. Good Start should not be fed to these children who are more highly sensitized.

INTRODUCTION

COW'S MILK (CM) PROTEIN HYDROLYSATE infant formulas have been used successfully in the management of children with preexisting cow's milk allergy (CMA).^{1,2} However, despite the fact the formulas have reduced antigenicity and allergenicity, none of them are nonantigenic or nonallergenic.⁽³⁻⁶⁾ The extensively

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hydrolyzed casein formulas (Alimentum,⁽⁷⁾ Nutramigen,^(8,9) Pregestimil⁽¹⁰⁾) and the less extensively hydrolyzed whey formulas (Alfaré,⁽¹¹⁾ Good Start⁽¹²⁾) have caused anaphylactic reactions in certain children with IgE-mediated immediate hypersensitivity. For these children who are highly sensitized, it is irrelevant to refer to the hydrolysate formulas as “hypoallergenic.” Misinterpretation of the term to mean completely safe could be dangerous. However, the CM protein hydrolysate formulas can be useful and are safe for those children with a lesser degree of IgE-mediated CMA.

We have studied children with mild (group 1A, topical reactors) IgE-mediated CMA, as designated by our previously published subclassification scheme using skin prick tests (SPT) to hydrolysate formulas.^(6,13) Thirteen children were challenge-positive to CM. They tolerated a whey hydrolysate formula (Good Start) when challenged with it and when fed Good Start daily for at least 2 weeks. Eleven of thirteen were challenge-positive to CM after the trial of Good Start. Two children outgrew their CMA during this interval.

MATERIALS AND METHODS

Background (skin testing, and classification)

As reported elsewhere,⁽¹³⁾ 50 children with IgE-mediated CMA were seen for allergy consultation in Rochester, New York, between January 1, 1989, and August 31, 1990. SPTs were done on their backs with commercially available CM infant formulas, purchased at the local supermarket, prepared according to the manufacturer's instructions on the can, frozen in aliquots, and thawed before use. Saline-albumin and histamine controls were used. A positive reaction was considered to be a wheal equal to or greater than 3 mm × 3 mm in diameter and equal to or greater than the positive histamine control. Based on positive reactions to CM, Good Start (CM whey hydrolysate by Carnation), and Nutramigen (CM casein hydrolysate by Mead-Johnson), each child was assigned to one of three subgroups.⁽⁶⁾ Group 1A ($n = 20$) were SPT positive only to CM. Group 1B ($n = 17$) were SPT positive to CM and Good Start but not to Nutramigen. Group 1C ($n = 13$) were SPT positive to CM, Good Start, and Nutramigen. There were no adverse reactions to the skin-testing procedure (Table 1).

Children in groups 1B and 1C differed from those in group 1A both immunologically and clinically despite the fact that all of the children had hives as part of their initial and subsequent allergic episodes with CM. Groups 1B and 1C had higher ($p = 0.0004$) serum IgE antibodies to CM and the major CM allergens (beta-lactoglobulin and casein) than those in group 1A (Table 1). When challenged with CM, groups 1B ($n = 9$) and 1C ($n = 4$) had more systemic respiratory cough/wheeze ($p = 0.005$) and rhinitis ($p = 0.013$) reactions than group 1A ($n = 13$). Those in group 1A had topical urticarial (100%) reactions (hives around the mouth or wherever milk touched the skin) and gastrointestinal (54%) vomiting reactions. They did not have systemic respiratory reactions (Tables 1 and 2).

In a separate double-blind placebo-controlled food challenge (DBPCFC) study with CM, 4 CM protein hydrolysate formulas (Good Start, Ultrafiltered Good Start, Nutramigen, Alfaré), and a soy protein formula (Isomil), 7/9 group 1A children developed contact urticarial lesions with CM but tolerated the other formulas; 2/9 who in previous open challenges with CM had contact urticaria no longer reacted to CM. One of these (1/9) who was clinically allergic to soy had a systemic urticarial and respiratory reaction to Isomil. In the same DBPCFC study, all children in group 1B ($n = 9$) and group 1C ($n = 5$) had respiratory or generalized urticarial reactions to CM or to one or more of the CM hydrolysate formulas. No reactions occurred to the soy formula control. Based on these experiences, we believe that the subclassification scheme, using readily available, inexpensive infant CM formulas for easily performed, safe prick skin testing is helpful in separating immediate topical reactors group (1A) from immediate systemic reactors (groups 1B and 1C).

Patient selection

With informed parental consent, 13 children (8 females, 5 males) in group 1A entered the present study. Their ages ranged from 10 months to 47 months (mean 20.8 months). All of them had been breastfed from birth and had developed multiple hives on their face or where milk touched their skin with their first feeding

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of CM. The reactions were of enough concern to prompt their primary care physicians to advise CM avoidance, to continue breastfeeding, or to use a soy formula. None of the children had a history of rhinorrhea, sneezing, stridor, cough, wheezing, generalized urticaria, or anaphylactic shock when fed CM. Gastrointestinal signs and symptoms were inconstant. None had a history of atopic dermatitis.

Challenge procedure

After fasting overnight and not having had any medications for 48 hours, starting at approximately 9 AM, the children had open challenges in the private office of Allergy, Asthma, Immunology of Rochester, P.C. The challenges were conducted by the head pediatric nurse (LBP), who previously had done more than 70 double-blind, placebo-controlled challenges with various CM formulas. For the present study, the children were first challenged with CM. If the challenge was positive, they were then challenged, on a subsequent day, with Good Start. If the Good Start challenge was negative, they were then offered Good Start daily for at least 14 days, after which they returned to the office to be rechallenged with CM. Increasing amounts of formula beginning with 1 mL were given, allowing 10 minutes between doubling doses to observe for a reaction and to record objective and subjective cutaneous, upper respiratory, lower respiratory, and gastrointestinal signs and symptoms. Pulse and respiratory rates also were monitored. Challenges were stopped if there were generalized hives, repetitive cough, stridor, wheezing, colic, vomiting, or perioral urticaria (two or more obvious wheals and flares). Challenges were otherwise continued until approximately 10 ounces (318 mL) of formula were consumed. Small amounts of formula were placed into the mouth with a calibrated syringe. Larger amounts were fed by cup. No attempt was made to prevent the children from touching their mouths and their faces. In fact, this was common.

Thirteen other children (2 females, 11 males) with IgE-mediated CM allergy (group 1B = 8; group 1C = 5) were challenged with Good Start as part of a companion double-blind, placebo-controlled CM hydrolysate challenge study. Their ages ranged from 10 months to 16 years. These challenges were done in the

TABLE 1. SKIN PRICK TESTS, SPECIFIC IgE AND TOTAL IgE IN 50 CHILDREN WITH IgE-MEDIATED COW'S MILK ALLERGY

<i>Test</i>	<i>Group (mean ± SEM)^a</i>			<i>p-value (Scheffe test)</i>		
	<i>IA n = 20</i>	<i>IB n = 17</i>	<i>IC n = 13</i>	<i>A vs B</i>	<i>A vs C</i>	<i>B vs C</i>
SPT histamine (mm ²)	14 ± 3	11 ± 2	17 ± 2	NS	NS	NS
SPT Cow's milk (mm ²)	74 ± 16	61 ± 11	135 ± 33	NS	NS	0.047
SPT Good Start (mm ²)	Neg	47 ± 11	155 ± 53	—	—	0.03
SPT Nutramigen (mm ²)	Neg	Neg	58 ± 10	—	—	—
sIgE ^b Cow's milk IU/mL	1.02 ± 0.19	10.59 ± 3.01	29.33 ± 3.49	0.016	0.000	0.000
sIgE β-Lactoglobulin IU/mL	0.60 ± 0.12	2.92 ± 0.75	12.69 ± 4.29	NS	0.0005	0.007
sIgE Casein IU/mL	0.54 ± 0.07	3.89 ± 1.29	11.07 ± 3.38	NS	0.0004	0.025
Total IgE IU/ml	142 ± 63	525 ± 207	652 ± 343	NS	NS	NS

^aSEM, standard error of mean; SPT, skin prick test; mm², area of wheal in millimeters; NS, not significant.

^bANOVA: sIgE (cow's milk): $F = 33.90$; $p = 0.0000$.

sIgE (β-lactoglobulin): $F = 9.421$; $p = 0.0004$.

sIgE (casein): $F = .248$; $p = 0.0004$.

clinical research unit of Strong Memorial Hospital, University of Rochester Medical Center. The same challenge protocol was followed. Informed consent was obtained from parents and assent from children. The research was approved by the Committee on Investigation of Human Subjects. These children had needles placed for intravenous access during the challenges.

Skin tests and blood tests

Skin tests and blood tests were performed a few days before the first CM challenge and after the second CM challenge. SPTs were done on the back. At 15 minutes, the wheals and flares were measured at their greatest diameter and at the midpoint crossing that diameter and recorded in millimeters. Ballpoint pen outlines of the reactions were transferred to a paper record using scotch tape. Subjects were tested with (1) diluent control (Hollister Stier, Division of Miles Laboratories, Inc., Elkhart, IN), (2) histamine control (Histrol, histamine phosphate 2.75 mg/mL, Center Laboratories, Port Washington, NY), Similac (Ross Laboratories), Good Start (Carnation), (5) Nutramigen (Mead Johnson), and (6) Isomil (Ross Laboratories). The infant formulas were prepared according to the manufacturers' instructions on the can and frozen in aliquots to be thawed for use. They were placed on the back as drops through which the skin was superficially abraded (plucked) with a straight pin. A new pin was used for each SPT to prevent carryover of antigen from one site to the next. The subjects and their skin test sites were observed constantly for 15 minutes. If a rapidly enlarging wheal was seen, the drops were quickly wiped off. No systemic reactions occurred in any children. Some group 1C

TABLE 2. FREQUENCY OF SIGNS AND SYMPTOMS IN COW'S MILK CHALLENGE

<i>Signs/symptoms^b</i>	<i>Melbourne^a</i>	<i>Rochester</i>			
	<i>Group 1 n = 27</i>	<i>Group 1 n = 26</i>	<i>1A^c n = 13</i>	<i>1B n = 9</i>	<i>1C n = 4</i>
Cutaneous					
Angioedema/urticaria	21 (78%)	26 (100%)	13 (100%)	9 (100%)	4 100%
Eczema	3 (11%)	1 (4%)	0 (0%)	1 (11%)	0 (0%)
Respiratory					
Rhinitis	2 (7%)	9 (35%)	1 (8%)	5 (56%)	3 (75%)
Conjunctivitis	0	4 (15%)	3 (23%)	0 (0%)	1 (25%)
Cough/wheeze	8 (30%)	10 (38%)	1 (15%)	6 (67%)	3 (75%)
Stridor	2 (7%)	1 (4%)	0 (0%)	1 (11%)	0 (0%)
Gastrointestinal					
Vomiting	9 (33%)	10 (38%)	7 (54%)	3 (33%)	0 (0%)
Diarrhea	4 (15%)	4 (15%)	2 (15%)	2 (22%)	0 (0%)

^aFrom Hill DJ, Firer MA, Shelton MJ, et al. Manifestations of milk allergy in infancy: Clinical and immunologic findings. *J Pediatr* 1986;109:270-276.

^bChi-square and Fisher's Exact Test:

Cough/wheeze: (B + C) vs A: Chi-square = 7.96; $p = 0.005$.

Rhinitis: (B + C) vs A: Chi-square = 6.11; $p = 0.013$.

Vomiting: (B + C) vs A: Chi-square = 1.46; $p = 0.226$.

^cGroup 1A, topical reactors.

Group 1B + 1C, systemic reactors.

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children were treated with antihistamines because of very large uncomfortable immediate skin test reactions. A positive reaction was considered to be equal to or greater than the histamine control and equal to or greater than 3 mm × 3 mm.

Specific IgE (IU/mL) to CM and serum total IgE (IU/mL) were determined by the 3M Fast-Plus method (3M Diagnostic Systems, Inc., Santa Clara, CA) on serum obtained before the first CM challenge and after the second CM challenge.

RESULTS

Skin tests

By definition, group 1A children were SPT positive only to CM (Similac), group 1B children were SPT positive to CM and to the whey hydrolysate (Good Start), and group 1C children were SPT positive to CM, to the whey hydrolysate (Good Start), and to the casein hydrolysate (Nutramigen). Group 1C had larger reactions to CM than group 1A or 1B, and group 1C had larger reactions to Good Start than group 1B (Table 1).

Specific IgE to CM

As previously reported,⁽¹³⁾ group 1A children had measurable specific IgE to CM, but the mean level was significantly lower than that for both groups 1B and 1C. This relationship held true in the present study (Table 1).

Challenge studies

Thirteen group 1A children had positive challenges to CM consisting of perioral urticaria (13/13) and vomiting (5/13) (Table 3). None had respiratory signs or symptoms or generalized urticaria. When challenged with Good Start, all of them (13/13) were able to tolerate 318 mL without any reactions. In contrast ($p = 0.03$), 8 of 13 children in group 1B/1C (1B = 3/8, 1C = 5/5) had immediate stridor, wheezing, and urticarial reactions when challenged with Good Start.

The 13 group 1A children consumed 4 to 24 ounces of Good Start formula per day for at least 14 days without any cutaneous, gastrointestinal, or respiratory reactions.

The 13 group 1A children returned for the second CM challenge, and 11/13 developed immediate perioral hives; 2/13 vomited, as they had done previously. None developed more severe cutaneous, gastrointestinal, or respiratory reactions. Two (2/13) did not react at all and can be considered to have outgrown their clinical sensitivity.

The group's mean SPT size to CM was the same ($p = 0.5$) before and after the challenge studies. The group's mean specific IgE to CM was the same ($p = 0.6$) before and after the challenge studies.

DISCUSSION

In this study, we have shown that children with group 1A IgE-mediated allergy to whole CM, manifested mainly by topical contact urticaria, did not react to a whey hydrolysate formula (Good Start) when challenged and were able to tolerate it during an open trial. Most of them (11/13) remained clinically allergic to whole CM. Their level of sensitivity, as measured by skin prick test wheal size, serum-specific IgE to CM, and extent of reaction to a repeat challenge with whole CM, did not change. Two children had negative second challenges to whole CM and can be considered to have outgrown their CMA. The role Good Start played in this process, if any, is unknown. Their SPTs to CM remained positive, and serum-specific IgEs to CM were unchanged.

In contrast ($p = 0.03$), in a companion study, we have shown that 8/13 (62%) of children with group 1B/1C IgE-mediated CMA react to small amounts of Good Start with systemic urticarial and respiratory reactions.

Thus, we believe that SPTs to CM, Good Start, and Nutramigen can be useful to distinguish group 1A from groups 1B and 1C and to select a formula that will be tolerated by children in group 1A. Good Start is a safe alternative to whole CM in children with mild, topical group 1A IgE-mediated CMA. It is not safe for all children with more severe, systemic types of reactions (groups 1B and 1C). Additionally, it is apparent that what is hypoallergenic for one group (1A) is not hypoallergenic for the other groups (1B and 1C).

Of the 50 children with IgE-mediated CMA referred to and evaluated by RHS between January 1, 1989, and August 31, 1990, 40% (20/50) were classified as group 1A, 34% (17/50) were group 1B, and 26% (13/50) were group 1C. Group 1A is probably underrepresented with respect to the population of children with IgE-mediated CMA. Because of their mild condition, they are less likely to be brought to the pediatrician's attention or less likely to be referred by the pediatrician for allergy evaluation and management than are those children with more severe CMA.

We and others have reported anaphylactic reactions to both whey (Alfaré,⁽¹¹⁾ Good Start⁽¹²⁾) and casein (Alimentum,⁽⁷⁾ Nutramigen,^(8,9) Pregestimil⁽¹⁰⁾) hydrolysate formulas. Because these reactions are uncommon, some health care providers may think they are nonexistent. We hope this article will alert them to this real possibility, which was described in 1956 by Dr. Jerome Glaser⁽¹⁴⁾ in Rochester, New York.

A hydrolyzed casein preparation as Nutramigen should provide, theoretically, a satisfactory milk substitute. In my experience, its use has been disappointing, although many of my colleagues have used it with very good results. Its taste is unacceptable to older children, diarrhea is frequent, and milk-sensitive babies do not commonly respond favorably. Probably the reason is that (some) infants may be so exquisitely sensitive to milk protein that they will react to it when present in such traces that it cannot be detected by the usual chemical or biological tests.

In the past, Dr. Glaser⁽¹⁵⁾ and his student colleague, Dr. Douglas Johnstone,⁽¹⁶⁾ proposed that soybean protein formulas or breastfeeding be used for the prophylaxis of atopy in infants and children and for the management of children with preexisting CMA. However, soy protein-based formulas are both antigenic and allergenic, with reports of up to 50% of children with CMA becoming sensitive to it.^(17,18) Of the 75 children with IgE-mediated CMA in the Rochester study, 7% (5/75) had acute reactions to soy formula, and 32%

TABLE 3. SUMMARY OF STUDIES ON 13 CHILDREN WITH GROUP 1A IgE-MEDIATED ALLERGY TO COW'S MILK

Patient identification				SPT ^a (mm ²)		IgE to CM (IU/mL)		Reaction to CM		Good ^c Start (days/oz)
No.	Initials	Sex	Age (mos.)	Pre ^b	Post	Pre ^b	Post	1st	2nd	
1	TM	M	17	9	15	0.77	0.51	POH, V ^d	POH	135/18
2	ER	F	17	120	45	4.22	5.24	POH, V	POH, V	120/12
3	GC	F	17	50	35	0.20	0.20	POH	POH	30/4
4	RP	M	16	45	40	0.20	0.20	POH	POH	60/24
5	JW	F	47	165	226	0.88	0.56	POH, V	POH, V	30/6
6	JM	F	16	9	25	1.81	0.37	POH, V	POH	30/20
7	EH	F	10	84	110	0.20	0.37	POH	POH	30/24
8	JG	F	30	110	45	1.16	1.38	POH	POH	14/4
9	LN	F	13	9	0	0.82	1.10	POH, V	POH	30/20
10	MS	F	12	9	9	0.44	0.20	POH	POH	34/20
11	PR	M	18	35	6	0.20	0.20	POH	POH	40/12
12	CP	M	21	100	35	1.47	1.67	POH	NR ^e	90/12
13	MM	M	36	6	6	0.30	0.35	POH, V	NR	30/15
Mean			20.77	57.77	49.75	0.97	0.95			

^aSPT, skin prick test; mm², area of wheal in square millimeters.

^bPre, before 1st CM challenge; Post, after 2nd CM challenge.

^cGood Start (days/oz), number days on Good Start/number of ounces consumed per day. *Note:* All patients tolerated Good Start (10 oz) when challenged and in open trial.

^dPOH, perioral hives; V, vomiting.

^eNR, no reaction when challenged with CM.

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(24/75) had positive RAST (equal to or > class 2) to soy.⁽¹³⁾ We are perplexed by the observation, in Rochester, that 91% (68/75) of children with IgE-mediated CMA were initially breastfed and the remaining 9% (7/75) were soy formula-fed before their reaction to the first feeding of CM at time of weaning. This strongly suggests that breastfeeding and soy formula feeding, as practiced today, do not prevent the development of IgE-mediated CMA and, in fact, may encourage it. Chandra et al.⁽¹⁹⁾ have reported success using a whey hydrolysate formula (Good Start) to feed infants at risk of developing atopy. A significant reduction in the development of atopic dermatitis occurred at 6, 12, and 18 months of age when these children were compared to breastfed and soy formula-fed infants.

Therefore, with all due respect, despite being Dr. Johnstone's student-colleague, the senior author of this article (RHS), based on his own experience and research, prefers to use hydrolysate formulas, including Good Start, in the management of carefully selected infants and children with mild, topical, group 1A IgE-mediated CMA. He will continue to encourage breastfeeding for all newborns unless those at risk for developing severe IgE-mediated CMA can be identified and alternative interventions have been proved.

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