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Clinical predictors for favorable outcomes in an oral immunotherapy program for IgE-mediated cow's milk allergy

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ABSTRACT

Background: Avoidance strategies in patients with cow's milk allergy occasionally fail to protect these patients from inadvertent exposures, leading to life-threatening reactions.
Objective: To assess the safety and efficacy of milk oral immunotherapy as an alternative therapeutic strategy.
Methods: Patients (n = 280, >4 years old) with IgE-mediated cow's milk allergy were enrolled into a milk oral immunotherapy program at a single hospital center. High-risk patients were not excluded. The treatment protocol consisted of 3 rounds of oral induction performed every 4 weeks. On day 1, a patient's reaction threshold was determined. On days 2 and 3, a tolerated starting dose below the threshold was confirmed. Day 4 mimicked the home treatment, which continued until the next induction.
Results: The median initial starting dose was 52.5 mg of cow's milk protein. Excluding those whose treatment failed in the first week (n = 5) or are still undergoing treatment (n = 15), 61.5% (160 of 260 patients) achieved 7,200 mg and 85.4% of patients were consuming at least 180 mg of milk protein. Reactions at home requiring the use of injectable epinephrine occurred in 15.7% of patients (44 of 280) and in 0.075% (58 of 77,098) of doses administered. Predictors for achieving a full dose in multivariate analysis included a starting dose higher than 30 mg of milk protein (odds ratio 4.6, $P < .001$), not requiring epinephrine during induction (odds ratio 5.2, $P < .001$) or home treatment (odds ratio 2.6, $P = .037$), and the lack of nonanaphylactic type symptoms (odds ratio 15.6, $P < .001$).
Conclusion: Milk oral immunotherapy, carried out in a highly controlled setting, is successful in protecting the overwhelming majority of patients from accidental exposures to cow's milk protein.

Introduction

In westernized countries, the published prevalence of food allergic reactions has increased and may affect as many as 6% of young children and 3% to 4% of adults. Ambulatory clinic visits, emergency department visits, and hospital-related discharge diagnoses related to food allergy have increased in recent years.[1–3] This medical burden is manifested by an estimated 125,000 emergency department visits in the United States each year for food allergy and approximately 15,000 food-induced anaphylaxis episodes across all age groups.[4] Most reactions in children younger than 5 years have been related to peanut and tree nut. In other countries, such as the United Kingdom and Australia, the pattern is similar, with food allergic reactions being the most common trigger of anaphylaxis, led primarily by reactions to peanut and tree nut and up to 10% related to cow's milk protein (CMP).[5,6] In contrast, a review of 40 pediatric food-related anaphylactic reactions in Israel found that 42.5% were related to CMP and 25% to peanut or tree nut.[7] Similarly, although most fatal reactions in the United States and United Kingdom were related to peanut and tree nut,[8–11] 3 of 4 recently reported cases of food-related mortality in Israel were related to CMP,[12] and an additional case came to the authors' attention after publication.

The present standard of care of patients with specific IgE to cow's milk allergy (CMA) emphasizes strict allergen avoidance and treatment with readily available injectable epinephrine when indicated.[13] Unfortunately, there is a high frequency of reactions owing to inadvertent exposures. A recent prospective 5-site study of 512 preschool-aged children reported an annualized reaction rate of 0.81%. Most of these reactions (71.2%) were related to milk and 11.4% were graded as severe.[14] Furthermore, based on several reports, 52% to 73% of children may recover from their IgE-mediated CMA by 4 to 5 years of age, with a sharp decrease of

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resolution thereafter.[15–17] Those with persistent IgE-mediated CMA are likely to have higher specific IgE to CMP and are likely to have a more severe phenotype.[15,17] Anaphylaxis-mediated fatalities in Israel were reported in older patients (6–26 years old), and although all had previous reactions after accidental exposures, none had experienced a life-threatening reaction.[12] These data imply that a large number of children with persistent CMA live with a physical and psychological burden of disease, including the risk of death.[13,18–20]

The potential for severe reactions, many of which can be life-threatening and some fatal, necessitate finding a modality that is more effective than following an allergen-free diet.[21] Milk oral immunotherapy (OIT) has shown promise as a mode of treatment and has shown efficacy in observational trials and a limited number of randomized controlled trials.[22–26] An OIT program for milk, peanut, and hen's egg was initiated in April 2010 at the Assaf Harofeh Medical Center in Israel. This report describes the clinical results of the first 280 patients who underwent milk OIT and were enrolled up to December 31, 2011.

Methods

This was an open-label individualized treatment program enrolling patients with persistent CMA who were followed through the Assaf Harofeh Allergy Clinic or referred by outside allergists. Inclusion criteria included an age at least 48 months, evidence of IgE-mediated allergy to CMP by positive skin prick test reaction and/or specific serum IgE, positive oral food challenge reaction, or a clinical history of a reaction after accidental ingestion in the previous year. For this study, these patients were defined as having persistent IgE-CMA.[15,27] High-risk patients, including those with a history of anaphylaxis, were not excluded. Anaphylaxis was defined as the involvement of at least 2 organ systems during a reaction. Patients with stable asthma being treated with daily controller inhaled steroid therapy or as needed were included. Exclusion criteria were uncontrolled asthma, a medical contraindication to receive epinephrine, or an inability to adhere to the protocol. Single skin prick tests to CMP were performed on the first day of treatment (1:10 w/v; ALK-Abello, Port Washington, New York). Skin prick tests were performed on the volar surface of the forearm with single peak lancets (Heinz Herenz, Hamburg, Germany) and wheal and flare sizes were measured after 20 minutes. Histamine 1 mg/mL (ALK-Abello) was used as the positive control and saline as the negative control, as previously described.[28] All patients enrolled up to December 2011 (n = 280) were reviewed. Patients participated for varying durations in the program, depending on their rate of progression to reach full desensitization, because dosing regimens were individualized. Analysis of their clinical status was performed on October 31, 2012. One patient started the program, dropped out, and then restarted. A complete blood cell count and an eosinophil count at the start of the program were obtained. Informed parental or patient (>18 years old) written consent for treatment was obtained from all participants. Committee approval was obtained for the publication of patient data according to the Declaration of Helsinki.

Milk OIT Protocol

The program consisted of monthly rounds of dose escalations performed in a day hospital setting at Assaf Harofeh Medical Center. During the first round, an initial determination of the maximal tolerated starting dose (SDo) for each patient was performed over a 4-day period (Table 1). During the second and third escalation rounds, up to a maximum of 4-fold was best tolerated. After each round, the achieved dose was consumed twice daily at home for 24 days. After the first 3 rounds, single-day escalations were performed during which the dose was increased by 50%. Monthly 50% increases were continued until full desensitization was achieved (240 mL of cow's milk = 7.2 g of CMP).

The first day of the initial visit included a modified challenge-desensitization protocol using fresh cow's milk. CMP doses started at 0.3 mg (1.0 mL of a 1:100 dilution) and escalated to 3.0 mg (1.0 mL of a 1:10 dilution), 15 mg (1.0 mL of 1:2 dilution), 30 mg (1.0 mL undiluted), 60 mg (2.0 mL undiluted), and 120 mg (4.0 mL undiluted) twice or until a clinical reaction occurred (eliciting dose; the protocol is presented in eTable 1 of the online repository). The reaction was treated and the patient was observed for a minimum of 90 minutes. On day 2, the goal was to determine the highest possible tolerated SDo. For that purpose, the two highest tolerated doses on day 1 were administered, followed by 2 doses formulated midway between the last tolerated dose and the eliciting dose (Table 1 presents a detailed example). On days 3 and 4, the objective was to verify that the maximal tolerated dose determined on day 2 was indeed safe and repeatable. For that purpose, on day 3, the dose before and 2 maximal tolerated SDo were administered; on day 4 the home treatment was mimicked and 2 maximal tolerated SDos were administered. Then, the maximum tolerated SDo was consumed twice daily at home for 24 days until the next round. If no reaction

Table 1
Example protocol of inductions 1, 2, and 3[a]

	Induction 1			Induction 2			Induction 3		
	Dose	Dose (mg)	Interval (min)	Dose	Dose (mg)	Interval (min)	Dose	Dose (mg)	Interval (min)
Day 1	1	0.3	10	1	45	90	1	180	90
	2	3	10	2	65	90	2	270	90
	3	15	15	3	80	90	3	330	90
	4	30	20	4	100	90	4	420	90
	5	60[b]	90[c]	5	120	90	5	540	90
Day 2	1	15	30	1	65	90	1	270	90
	2	30	60	2	90	90	2	390	90
	3	45	90	3	120	90	3	480	90
	4	45	90	4	150	90	4	600	90
				5	180	90	5	720	90
Day 3	1	30	60	1	120	90	1	480	90
	2	45	90	2	180	90	2	720	90
	3	45	90	3	180	90	3	720	90
Day 4	1	45	90	1	180	90	1	720	90
	2	45	90	2	180	90	2	720	90

[a]This example represents a patient who reacted to 60 mg in the first round of induction and then received a maximum 4-fold increase in rounds 2 and 3.
[b]Reaction at 60 mg.
[c]The interval after the last dose on each day was the observation period before discharge.

occurred on the first induction day, the second day began at 120 mg and the dose was doubled every 30 minutes until a reaction occurred (eTable 1). By the second day, 98% of patients exhibited a reaction. An immediate reaction (<90 minutes) involving a cutaneous, respiratory, gastrointestinal, or systemic response was characterized as mediated by IgE. Nonanaphylactic type reactions included psychological food aversion and abdominal pain with or without vomiting, not directly related to the consumption of a dose. All procedures are performed with resuscitation equipment and an adjacent emergency department available for the treatment of possible severe adverse reactions.

Safety Measures

Safety measures included assigning each patient a unique color code, in addition to their name labeling, for accurate dosage administration. Anticipatory home treatment guidance included supervision by a parent for at least 60 minutes after dosage, avoidance of exercise for 120 minutes after dosing, empiric dose reduction with upper respiratory infections, aggressive treatment of asthma, avoidance of nonsteroidal anti-inflammatory drugs, and awareness of possible problems around menses. No dose increases were allowed at home. All parents (and patients if old enough) received a review of the EpiPen (Mylan Specialty, LP, Basking Ridge, New Jersey) and had to demonstrate competence in administration using a demonstration device. Two up-to-date EpiPens had to be available at all times, in addition to antihistamines, a powered nebulizer for the administration of bronchodilators, and/or nebulized epinephrine. Instructions included the liberal/early use of the EpiPen and its use initiated before any call for medical assistance. Daily E-mail reports were required from all participants to verify dosage compliance and to record adverse reactions or treatments required during the home therapy phase. A staff physician was on call at all times for consultation and appropriate dosage adjustments were made before any further doses were administered.

CMP Preparation

The dosing regimen was determined by the physician and a written order was sent to the laboratory for CMP dose preparations up to 90 mg. All CMP doses were prepared from a stock of powdered formulas of Materna Mehadrin Stage 3 (Maternal Industries, Maabaroth, Israel) reconstituted to 45 mg/mL of CMP with sterile water. Each 100 g of powder contained 15 g of CMP. For doses lower than 90 mg, parents received a month's supply of prepared frozen single aliquots for administration at home. For doses of at least 90 mg of CMP, 3% fat milk (30 mg/mL of CMP) was obtained and administered by the parents.

Statistics

Statistical analyses were performed with SPSS 16 (SPSS, Inc, Chicago, Illinois). Patients who completed the program and achieved the full treatment dosage of 7,200 mg (240 mL) of cow's milk were compared with those who did not achieve a full dose. Continuous variables were abnormally distributed and therefore analyzed using the Mann-Whitney nonparametric test. The Fisher exact test was used to analyze differences in categorical variables between groups. Multivariate logistic regression analysis was performed to analyze the effect of multiple risk factors on reaching full dosage and odds ratios were determined. All analyses were 2-tailed and a P value less than .05 was considered significant.

Results

Two hundred eighty patients were enrolled up to December 2011. The median age was 7.5 years (range 4–27), 60% were male patients, and 179 of 280 (64%) had a physician diagnosis of asthma. Approximately half the patients (145 of 280) were sensitized to house dust mite and 46 of 280 (16.4%) had an additional food allergy. Most patients had exhibited severe reactions to CMP, manifested by a history of anaphylactic reaction (73%), emergency department visits (59%), hospital admission (25.4%), and having received epinephrine (43%), before initiating milk OIT. eFigure 1 presents the SDo of the treated patients. Fifty percent of patients (140 of 280) had an SDo no higher than 45 mg of CMP (eFig 1). This is equivalent to 1.5 mL of whole milk, providing a clinical indicator of the severity in this cohort.

Treatment results categorized according to a patient's clinical status are presented in Figure 1. Five patients had primary failures, defined as failed milk OIT during the first induction week (3 owing to extreme sensitivity to CMP, ie, <10 mg, and 2 others owing to parental or psychological issues). Fifteen patients continue to receive increasing amounts of CMP and their final status has not been determined. Of the remaining patients, 160 of 260 (61.5%) could freely consume milk (>7.2 g) or milk products (>7,200 mg) and 66 tolerated smaller amounts (62 of 66, >180 mg). Thus, 85.3% (226 of 260) were consuming at least 180 mg of CMP or the equivalent of 6 mL of milk. Five patients progressed to full consumption within the first week; thus, it is unclear whether they were truly desensitized or were tolerant to milk before the onset of the treatment program. However, because the results without these 5 patients were not significantly different, they were included in all subsequent analyses.

An additional 34 patients (12.1%) had secondary failures and stopped milk OIT later in the program (>1 week). Reasons for secondary failure were multiple. Sixteen had recurrent anaphylactic type reactions, 10 had psychological food-aversion behaviors, and 8 developed gastrointestinal symptoms with peripheral blood eosinophilia (>1,400). In all the latter 8 patients, resolution of symptoms and laboratory findings occurred after discontinuation of CMP.

The IgE-mediated reactions were expected to occur during the determination of a patient's threshold and 128 patients (45.7%) received epinephrine during induction cycles. In the home dosing phase, a reaction was reported for 1,494 of 77,098 doses (1.9%), of which 476 were not treated, 960 required treatment with an antihistamine alone or a bronchodilator, and 58 required the use of injectable epinephrine. The latter 58 reactions occurred in 15.7% of patients (44 of 280).

Factors affecting whether patients were able to consume full amounts of CMP included pretreatment parameters, such as the presence of physician-diagnosed asthma, CMP skin prick wheal

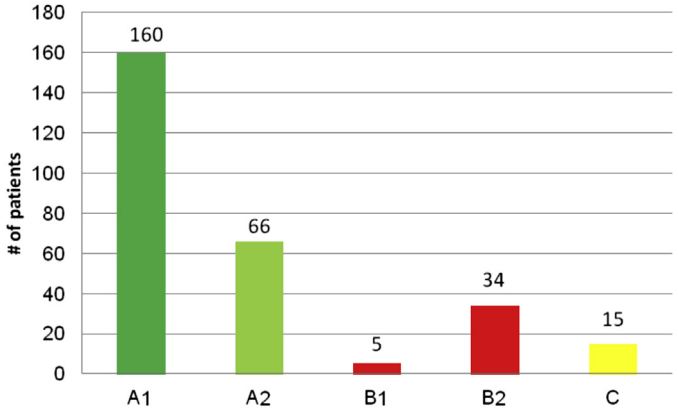

Figure 1. Clinical efficacy of milk oral immunotherapy. Patients are grouped according to their clinical status. In total, 280 patients were enrolled. A1, consumes more than 7,200 mg; A2, consumes limited amount; B1, primary failure; B2, secondary failure; C, active treatment in continuation protocol.

Table 2
Comparison of patients able to achieve the full dose of CMP with those unable to do so

Parameters	Full dose (n = 160)	Did not achieve full tolerance			*P* value[a]
		Completed treatment		Still in treatment (n = 15)	
		Partial dose of CMP (n = 66)	No CMP consumption (n = 39)		
Pretreatment					
Age (mo)[b]	92.5 (42–328)	93 (45–242)	79 (48–278)	84 (49–180)	.69
Male patients	63.8%	51.5%	53.8%	73.3%	.14
Asthma	43.1%	71.2%	64.1%	40%	<.001
HDM allergy	43.8%	51.5%	48.7%	73.3%	.2
CMP wheal size (mm)[b]	7 (2–18)	8 (4–16)	8 (4–17)	9 (4–14)	<.001
Other food allergies	18.1%	16.7%	13.2%	6.7%	.42
Anaphylaxis	63.8%	90.9%	82.1%	93.3%	<.001
Admission	19.4%	39.4%	25.6%	26.7%	.009
Emergency department visits	50.6%	72.7%	61.5%	93.3%	.001
Epinephrine	37.5%	53%	38.5%	71.4%	.04
During treatment					
Starting dose (mg)[b]	120 (10–7,200)	22.5 (12–960)	22.5 (0–7,200)	22.5 (12–90)	<.001
Current dose (mg)[b]	7,200 (3,600[c]–7,200)	600 (120–4,050)	0	1,500 (90–3,900)	<.001
Treatment duration (d)[b]	188 (2–816)	204.5 (59–638)	100 (1–394)	428 (369–981)	.35
Epinephrine (induction)	25.6%	71.2%	64.1%	86.7%	<.001
Epinephrine (home)	7.5%	27.3%	39.5%	13.3%	<.001
Non-anaphylactic reaction	5%	19.7%	38.5%	20%	<.001

Abbreviations: CMP, cow's milk protein; HDM, house dust mite.
[a] *P* values comparing patients who achieved the full dose with those who did not.
[b] Abnormally distributed continuous variables are presented as median (range).
[c] Patient achieved the full dose (7,200 mg) but over time decreased maintenance to 3,600 mg.

size, history of anaphylaxis, hospital admission, emergency department visit, and the use of epinephrine (Table 2). Parameters during treatment that were found to predict achieving full consumption included a higher SDo, not using epinephrine during induction or at home, and the absence of nonanaphylactic reactions (Table 2).

The most important independent parameters as calculated with multivariate analysis to predict achieving the full dose included an SDo higher than 30 mg of CMP, not requiring epinephrine during induction or home treatment, and not developing nonanaphylactic reactions (Table 3). The effect of a higher tolerated SDo after the first induction on the proportion of patients able to freely consume CMP (>7,200 mg) is shown in Figure 2A. Interestingly, although IgE-mediated type reactions requiring epinephrine use were significantly more frequent in the more sensitive patients with a lower SDo ($P < .0001$; Fig 2B), nonanaphylactic reactions occurred in comparable frequency regardless of the SDo ($P = .91$; Fig 2B).

Discussion

This report describes a large cohort of milk-allergic patients undergoing milk OIT for at least 10 months. Patients with a history of anaphylaxis were not excluded. The present study strengthens the understanding of the clinical factors that predict which patients undergoing milk OIT might be able to achieve full consumption of CMP. For example, the ability to tolerate an initial SDo higher than 30 mg, not requiring epinephrine during induction or home dosing, and the lack of nonanaphylactic reactions can provide very useful information to parents and patients regarding their milk OIT outcome expectations.

Table 3
Logistic regression analysis for achieving full tolerance to cow's milk protein

Parameter	OR for achieving full tolerance	CI	*P* value
Starting dose ≥30 mg	4.6	2.2–9.6	<.001
Not requiring epinephrine at induction	5.2	2.6–10.5	<.001
Not requiring epinephrine at home	2.6	1.1–6.2	.037
Not experiencing nonanaphylactic reaction	15.6	5.5–44.5	<.001

Abbreviations: CI, confidence interval; OR, odds ratio.

Sixty-two percent of patients in this study achieved full consumption (7,200 mg), in line with the cumulative statistics compiled in the latest Cochrane review for milk OIT, despite the different protocols used.[29] Clinical sensitivity has been related to small eliciting doses,[30,31] yet the present clinical efficacy was achieved, although 50% of this cohort had an SDo no higher than 45 mg of CMP. Another indicator of severity in this cohort is that most (73.5%) had a history of systemic reactions, 43% of which were treated with epinephrine. In contrast to other investigators,[30] the authors did not find a relation between age as an independent factor and the ability to achieve full consumption during milk OIT. Of note, even in the most severe group, those with an SDo of 10 to 15 mg, 12 of 56 (21.4%) were able to attain full consumption of CMP. Furthermore, 85% of patients were able to consume higher than 180 mg of CMP, an amount larger than the reported lowest threshold doses of CMP eliciting a reaction.[32] This dose is presumed to be minimally protective against accidental CMP exposures. For example, in the 3 fatalities related to CMP that occurred in Israel, an estimated 180 mg or less was ingested.[12]

Although milk OIT is clinically efficacious, its benefits in protecting against purposeful and accidental exposures must be clearly weighed against the risks associated with reactions that are secondary to treatment. The likelihood of these exposures in preschool-aged children in a prospective study has been recently described as high as 71% over the 3-year period analyzed.[14] Alarmingly, 11.4% of reactions were graded as severe, whereas only approximately one third were treated with epinephrine. The anaphylaxis-mediated fatalities in Israel were reported in older patients (6–26 years old), and although all had previous reactions after accidental exposures, none had developed a life-threatening reaction and epinephrine was not administered during the fatal anaphylactic attack.[12] In contrast, in the present milk OIT program, the reaction rate requiring epinephrine treatment during home therapy was 0.075% of doses administered, occurring in 44 of 280 patients (15.7%). The frequency of epinephrine treatments may have been positively influenced by the encouragement for the liberal/early use of epinephrine in the anticipatory guidance sessions. By comparison, 0.2% of total home doses[22] and 6.7%[23] to 23%[24] of patients required epinephrine treatments in other randomly controlled milk OIT trials. The severity of IgE-mediated events during OIT may be related to the level of serum specific IgE to CMP.[33]

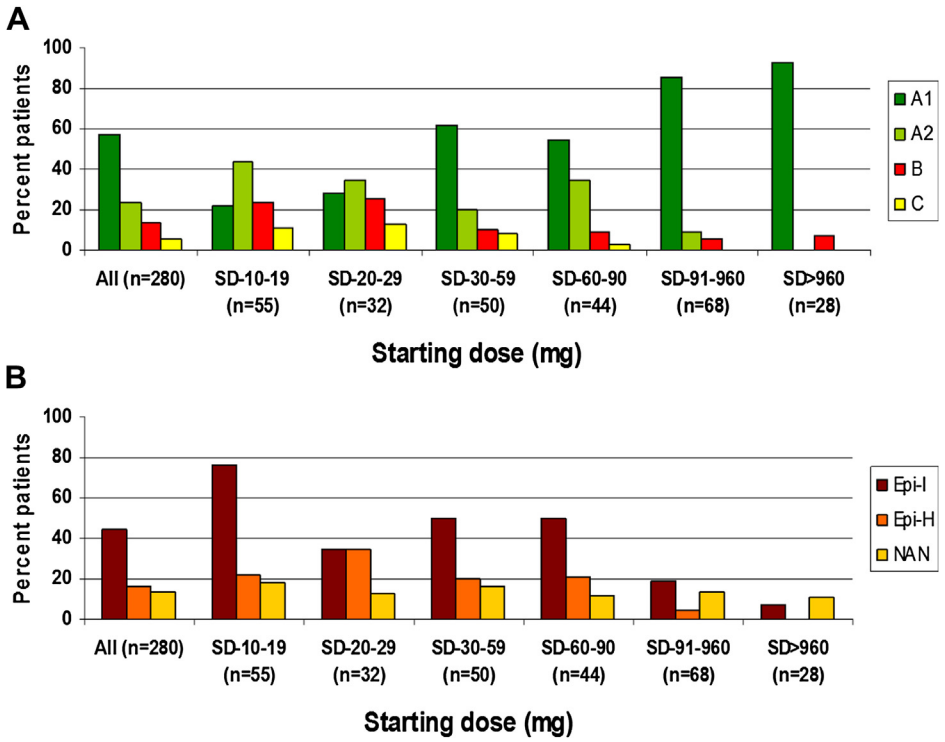

Figure 2. (*A*) Clinical status and (*B*) proportion of adverse events reported by patients stratified by their initial starting dose (SD). The number of IgE-mediated reactions requiring epinephrine during induction and home therapy differed between groups ($P < .0001$), whereas the number of nonanaphylactic (NAN) type reactions did not differ significantly between groups ($P < .91$). A1, consumes more than 7,200 mg; A2, consumes limited amount; B, primary and secondary failures; C, active treatment in continuation protocol; Epi-H, epinephrine treatment during home treatment; Epi-I, epinephrine treatment during induction.

Another important but less frequent reaction was non–IgE-mediated gastrointestinal complaints associated with increased peripheral blood eosinophilia. This occurred in 8 patients and will be the subject of a separate article addressing this issue. In 3 cases reported by Sanchez-Garcia et al,[34] the eosinophilic esophagitis induced by milk OIT resolved histologically after discontinuation of CMP. Thus, although clinicians should be aware of this potential side effect of milk OIT, it appears to be clinically manageable.

This treatment program was performed in a hospital-based setting in accord with all criteria of a research program. Nevertheless, by its very nature, a treatment program differs markedly in its approach to the patient. For example, each patient had an individualized dosing regimen that allowed patients to become desensitized at their own pace and laboratory parameters were drawn only when clinically indicated. Thus, specific IgE was not performed in most of the present patients. More than 98% of patients had positive challenge reactions to milk immediately before or during the first 2 days of treatment. All had a positive skin prick test reaction. In addition, all the present patients were older than 4 years (up to 27 years), an age when spontaneous recovery is less likely.[15,35] Taken together, these patients at the onset of the program had IgE-mediated CMP allergy; moreover, although no control group was followed, it is unlikely such a large proportion would have spontaneously recovered during the program duration.

Several areas of research remain to be explored in this burgeoning field of milk OIT. One major question is whether the desensitized state induced by milk OIT translates to true tolerance after several years of treatment. A second area of research is whether the introduction of dairy or other sources of dietary calcium in these patients promotes their bone density and mineral content.[36] Another relatively untouched investigation, but critical for the risk–benefit analysis of milk OIT, is the potential lifting of the incredible psychological burden experienced by patients and caretakers alike, as has been recently described.[37]

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Supplementary Data

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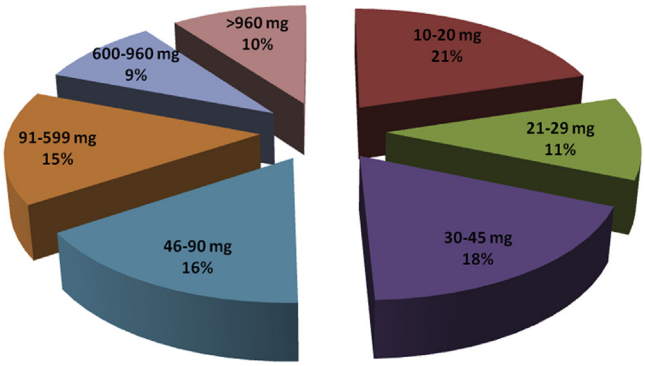

eFigure 1. Maximal individualized tolerated dose of cow's milk protein, presented as the percentage of patients and the amount of cow's milk protein (milligrams) tolerated after the first induction. Fifty percent of patients tolerated less than 45 mg of cow's milk protein.

eTable 1
Initial milk oral immunotherapy induction protocol

	Dose	Dose (mg)	Interval (min)
Day 1	1	0.3	10
	2	3	10
	3	15	15
	4	30	20
	5	60	20
	6	120	60
	7	120[a]	90[b]
Day 2	1	120	30
	2	180	30
	3	300	30
	4	480	30
	5	720	30
	6	960	30
	7	1,440	30
	8	1,920	90[b]

[a]If no reaction occurs on day 1, the protocol continues to day 2.
[b]Observation time before discharge.