Oral immunotherapy for cow's milk allergy with a weekly up-dosing regimen: a randomized single-blind controlled study

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Background: Cow's milk allergy (CMA) in children is a important problem in medical practice. Oral desensitization has been proposed as a therapeutic approach, but current protocols are time-consuming and impractical.

Objectives: To establish a patient-friendly desensitization regimen with weekly up-dosing and to evaluate it in a randomized controlled trial.

Methods: Thirty children with IgE-mediated CMA confirmed by double-blind placebo-controlled food challenge were equally randomized to desensitization with CM or soy milk as control. The weekly up-dosing lasted 18 weeks. The occurrence and severity of reactions after each dose was evaluated, and the desensitization was stopped if severe reactions occurred. Specific IgE and IgG4 levels to CM were measured at baseline, after 8 weeks, and at the end of the study. The double-blind food challenge was repeated once the desensitization was completed or after premature discontinuation.

Results: Two active and 1 control patient dropped out. Full tolerance to CM (200 mL) was achieved in 10 active patients and partial tolerance in 1. Two active patients discontinued the desensitization after experiencing severe reactions, whereas no reactions occurred in controls, whose sensitivity to CM remained unchanged. A significant increase in specific IgG4 levels was found only in the active group.

Conclusions: This weekly up-dosing desensitization protocol for CMA performed under medical supervision was effective and reasonably safe and induced consistent immunologic changes.

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INTRODUCTION

Among food allergies, cow's milk allergy (CMA) is the most relevant in the pediatric age group owing to its prevalence, the practical difficulties in management, the emotional burden for children and parents, and the nutritional implications. Currently, the management of CMA is primarily based on the complete avoidance of CM. This approach is associated with impaired quality of life for allergic children and their families.[1,2] In addition, it is difficult to achieve complete avoidance because milk proteins can be present in small amounts or even as hidden allergens in a variety of processed foods. This may lead to unexpected exposure and possibly severe reactions. The present interventions for CMA include avoidance maneuvers and education regarding the proper indications for and use of autoinjectable epinephrine. Among the CM substitutes most frequently used are soy formulas and extensively hydrolyzed formulas of casein and whey. These substitutes have an acceptable nutritional value, but hydrolyzed formulas often have an unpleasant taste and are expensive and soy formulas have themselves the potential to evoke allergic reactions.

It has been shown that infants with CMA but without detectable specific IgE levels to CM have a higher spontaneous recovery rate compared with infants with high levels of specific IgE toward milk proteins (IgE-mediated CMA).[3-5] Oral desensitization or immunotherapy, also referred to as "tolerance induction," has been suggested as a suitable approach to reduce clinical symptoms and modify the immune response to allergens, and this was also confirmed in the case of CMA.[6-11] Oral immunotherapy is usually performed starting with very low amounts of milk, which are then slowly increased until an amount comparable with the usual daily intake is reached. Afterward, milk is given daily to maintain the tolerant state. The protocols that have been published usually have a very long duration[6,12] or require hospitalization of the child for several days.[6,7] As such, they are considered, to some extent, to be impractical. Based on these considerations, we attempted to set up a more patient-friendly and easy-to-perform oral desensitization using a weekly up-dosing regimen. The feasibility of this approach was demonstrated in a previous open exploratory study.[13] The present trial was undertaken to confirm in a randomized and con-

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trolled manner the clinical efficacy and safety of this approach.

METHODS

Overall Design

This study was designed as a randomized, single-blind, soy milk–controlled trial with 2 parallel groups. Children 4 years or older with demonstrated IgE-mediated CMA were enrolled and were randomized to receive either active oral immunotherapy or matched soy formula**.** The efficacy of the desensitization was evaluated during a 4-month period by identifying the maximum tolerated dose of milk or, ideally, 200 mL. The ethics committee of the Department of Pediatrics, University of Messina, approved the study, and all the parents of the children signed an informed consent form.

Patients and Diagnosis

Children of both sexes aged 4 to 10 years with demonstrated IgE-mediated CMA were enrolled at the allergy units of the departments of pediatrics of Messina and Catania university hospitals between January 1, 2006, and and December 31, 2008. The diagnosis of CMA was based on (1) clinical history, (2) demonstration of the presence of CM specific IgE by means of skin testing and CAP-RAST assay, and (3) a positive double-blind placebo-controlled food challenge (DBPCFC) result. None of the patients had a positive clinical history or suspected adverse reactions to soy formula or positive skin test results or serum specific IgE levels to soy. This was required to ensure the safety of DBPCFC and the desensitization protocol with soy formula as controls. Sensitization to other foods was an exclusion criteria as well.

Skin prick tests were performed on the volar surface of the forearm with commercial extracts of whole milk, α-lactalbumin, β-lactoglobulin, and casein (all f rom Lofarma Spa, Milan, Italy). A prick-prick test with undiluted fresh CM and soy formula was also performed. A wheal of 3 mm or greater was considered positive. The DBPCFC was conducted before randomization and at the end of treatment, before revealing the blinding. It was performed at the clinics under medical supervision and with resuscitation facilities immediately available. Fresh CM or soy formula (Humana Sinelac, Milan) was administered at increasing doses of 0.1, 0.3, 1, 3, 10, 30, and 100 mL in a double-blind manner, with 30 minutes between doses. The challenge procedure was stopped when the highest dose was reached or if any of the following occurred: urticaria, angioedema, wheezing, rhinitis, vomiting, diarrhea, abdominal pain, exacerbation of atopic dermatitis, wheezing, rhinitis, or anaphylactic shock. After completing the DBPCFC procedure, children were observed for at least 6 hours and then were discharged. Rescue medications, to be given according to medical judgment, included diphenhydramine, prednisolone, adrenaline, and inhaled salbutamol.

Oral Immunotherapy Protocol

Oral immunotherapy involved the administration of increasing amounts of CM (or soy milk) at weekly intervals starting with 1 drop of whole milk diluted 1:25. The dose was doubled every week at the clinic until week 18 to achieve an intake of 200 mL in approximately 4.5 months. Soy milk was the control treatment. The doses were prepared blinded to the investigators by a nurse according to a computer-generated randomization list so that the physicians remained blinded to the treatment. The desensitization protocol, entirely performed at the clinics in an ambulatory regimen, is summarized in Table 1.

After receiving the dose, the children were observed and were considered to have a positive reaction if 1 or more of the following symptoms appeared: urticaria, exacerbation of eczema ($\geq$10-point increase in SCORing Atopic Dermatitis score), angioedema or generalized urticaria, vomiting, diarrhea, rhinitis, severe conjunctivitis, or anaphylactic reactions. If symptoms were judged as mild (abdominal pain, erythema, throat itching, or gritty eyes), no action was taken and the protocol was continued. When moderate or severe symptoms appeared, an appropriate medical treatment was given.

CM had to be avoided in the desensitization protocol. Oral antihistamine use was not permitted until the up-dosing period was completed. If an illness occurred (eg, the common cold or fever) during the desensitization, appropriate therapy was given and the weekly increase in the dose was postponed.

Immunologic Assays

Blood samples were collected before randomization, when the dose of 8 mL was reached (week 13), and at the end of the study. Specific IgE and specific IgG4 to CM, α-lactalbumin, β-lactoglobulin, and casein were assayed using the ImmunoCAP System (Phadia Diagnostics, Uppsala, Sweden).

IgG4 to CM could not be directly measured because of interfering IgG antibodies specific for bovine albumin in

Table 1. Oral Immunotherapy Protocol

Day/week	Dose No.	Volume
1/1	1	1 drop[a]
7/2	2	2 drops[a]
14/3	3	4 drops[a]
21/4	4	8 drops[a]
28/5	5	16 drops[a]
35/6	6	32 drops[a]
42/7	7	64 drops[a]
49/8	8	5 drops[b]
56/9	9	10 drops[b]
63/10	10	20 drops[b]
70/11	11	2 mL[b]
77/12	12	4 mL[b]
84/13	13	8 mL[b]
91/14	14	16 mL[b]
98/15	15	32 mL[b]
105/16	16	64 mL[b]
112/17	17	128 mL[b]
119/18	18	200 mL[b]

[a] Cow's milk diluted 1:25.
[b] Undiluted CM.

most sera. Therefore, the sum of α-lactalbumin, β-lactoglobulin, and casein specific IgG4 antibody levels was used as a surrogate measure of IgG4 to CM. The lower limit of assay detection was 0.35 kU/L for specific IgE and 0.3 μg/mL for specific IgG4.

Statistical Analysis

No formal calculation of the sample size could be made because no quantitative data about the clinical outcome could be hypothesized. The number of patients was chosen according to similar articles available in the literature. The Fisher exact test was used to compare the clinical characteristics of the 2 groups at baseline, except for age, which was compared using the *t* test. Immunologic variables were analyzed using the Wilcoxon and Mann-Whitney signed rank tests for intragroup and intergroup comparisons, respectively. All the tests were 2-tailed, and $P < .05$ was considered significant.

RESULTS

Clinical Results

The disposition of all patients considered for the study is summarized in Figure 1. Thirty children who fulfilled the inclusion and exclusion criteria were enrolled in the study and were equally randomized to active desensitization or control intervention. The clinical characteristics of the participants at randomization are given in Table 2. There were 2 dropouts in the active group and 1 in the control group (their parents withdrew their consent early in the study for personal reasons and not because of the desensitization procedure).

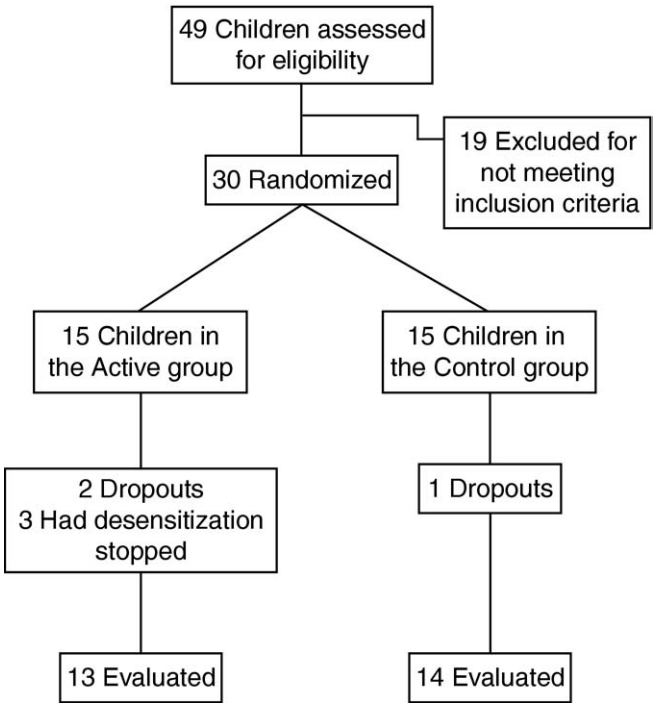

Figure 1. Study design and patient disposition.

Table 2. Demographic and Clinical Characteristics of the 30 Enrolled Children at Baseline[a]

	Active group (CM) (n = 15)	Control group (soy milk) (n = 15)
Sex, M/F, No.	8/7	9/6
Age, median (range), y	9 (4–12)	10 (4–13)
Duration of CM allergy, mean (SD), y	6.9 (3.2)	7.4 (3.7)
Atopic dermatitis, No.	3	3
Urticaria/angioedema, No.	4	3
Asthma, No.	1	1
Multiple symptoms, No.	5	7
Anaphylaxis, No.	2	1
Baseline CM specific IgE, median (range), kU/L	32.7 (8.8–124.6)	25.4 (5.3–97.3)
Baseline CM specific IgG4, median (range), μg/mL	4.5 (1.1–7.9)	3.1 (1.4–4.7)

Abbreviation: CM, cow's milk.

[a] The *P* values are not significant for all between-group comparisons.

The clinical results of the desensitization are summarized in Table 3. One patient achieved only partial tolerance because at the dose of 64 mL she developed urticaria, angioedema, and cough and received intramuscular antihistamines and corticosteroids. In this patient, the desensitization was stopped for ethical reasons. This patient, who previously experienced symptoms even with minimal amounts of CM, can now eat CM-containing cakes, snacks, delicatessen foods, and ice cream and can drink moderate amounts of CM without symptoms. At the DBPCFC, his threshold dose increased from 1 to 30 mL (cumulative, 45 mL). One patient experienced urticaria, rhinitis, throat pruritus, vomiting, and circulatory collapse with 4 mL. He promptly recovered after intramuscular adrenaline and antihistamine administration and intravenous corticosteroid treatment. A third patient failed to achieve tolerance because 2 mL of CM provoked rhinitis, cough, asthma, generalized urticaria, and laryngeal edema. He received intramuscular adrenaline and corticosteroids, oral antihistamines, and inhaled salbutamol and promptly recovered. In the 2 latter children, there was no appreciable change in the threshold dose in the DBPCFC (Table 4).

The remaining 10 children (77%) reached the 200-mL dose and, therefore, achieved full tolerance without adverse effects (Table 3). None of the 15 controls receiving soy milk had symptoms during the study. The results of the DBPCFC are given in Table 4. It is apparent that the control patients maintained unchanged their clinical response to CM, whereas the 10 children with successful desensitization had a negative DBPCFC result. The DBPFC was also repeated in the 3 children who had discontinued the protocol, and it remained positive in 2 of them. Approximately 6 months after the trial, no clinical changes had occurred in the patients, who continued to tolerate CM well.

Table 3. Results of Specific Oral Immunotherapy With CM

Patient No.	Age at the desensitization	Symptoms during CM desensitization	Dose of CM that elicited symptoms, mL	Action taken	Outcome of CM desensitization
1	10 y 3 mo	Rhinitis, cough, asthma, generalized urticaria	2	Adrenaline, corticosteroids, antihistamines, salbutamol, protocol stopped	Failed
2	9 y 2 mo	Abdominal pain, throat pruritus	128	Antihistamine, corticosteroid	Tolerated 200 mL of whole CM
3	5 y 9 mo	Generalized urticaria, angioedema, cough	64	Antihistamine, corticosteroid, protocol stopped	Partial tolerance, up to approximately 100 mL
4	7 y 1 mo	Throat pruritus, gritty eyes	32	None	Tolerated 200 mL of whole CM
5	6 y 4 mo	Abdominal pain, gritty eyes, watery eyes	128	None	Tolerated 200 mL of whole CM
6	9 y 5 mo	Transient erythema (face and hands)	128	None	Tolerated 200 mL of whole CM
7	10 y 1 mo	None	NA	None	Tolerated 200 mL of whole CM
8	6 y 3 mo	Abdominal pain, gritty eyes	64	None	Tolerated 200 mL of whole CM
9	5 y 4 mo	None	NA	None	Tolerated 200 mL of whole CM
10	8 y 4 mo	Rhinitis, urticaria, cough, hypotension, dyspnea	4	Adrenaline, corticosteroids, salbutamol, antihistamine, protocol stopped	Failed
11	4 y 8 mo	None	NA	None	Tolerated 200 mL of whole CM
12	6 y 2 mo	Abdominal pain	64	None	Tolerated 200 mL of whole CM
13	7 y 5 mo	Abdominal pain, gritty eyes	32	None	Tolerated 200 mL of whole CM

Abbreviations: CM, cow's milk; NA, not applicable.

Immunologic Variables

No significant difference in IgE levels between the active and control groups was observed at 13 or 18 weeks vs baseline (Fig. 2). However, in 5 children in the active group, specific IgE levels displayed a clear increase when the intermediate dose of 8 mL was reached, but they returned to near baseline values at the end of the study. The 3 children with serious adverse events during desensitization had an increase in specific IgE levels from baseline of approximately 85% (mean [SD] before vs after: 34.8 [7.6] vs 66.6 [8.1] kU/L). In the active group, mean (SD) serum IgG4 levels increased from baseline (4.52 [3.4] μg/mL) to week 18 (23.8 [5.3] μg/mL) ($P = .003$). Such an increase was not seen in the control group (3.13 [1.6] vs 4.37 [1.7] μg/mL, respectively) (Fig. 3). The intergroup comparison also confirmed a significant difference in favor of the active CM group vs controls at 18 weeks (mean [SD], 23.8 [5.3] vs 4.3 [1.7] μg/mL; $P < .01$).

Table 4. Results of the Double-Blind, Placebo-Controlled Food Challenge[a]

Patient No.	Active group		Control group	
	Baseline	End of the study	Baseline	End of the study
1	0.3	3 mL	3	10
2	3	Negative	3	1
3	1	30	1	1
4	3	Negative	3	3
5	10	Negative	10	10
6	3	Negative	3	10
7	10	Negative	0.3	1
8	3	Negative	30	30
9	10	Negative	3	3
10	0,3	3	10	10
11	30	Negative	30	30
12	1	Negative	1	1
13	1	Negative	3	3
14	10	Dropout	10	3
15	30	Dropout	3	Dropout

[a] Data are given as milliliters of milk that elicited symptoms.

Safety Data

The safety results during the double-blind treatment are summarized in Table 3. As mentioned previously herein, in 3 patients, severe events occurred and the desensitization was stopped. Three patients concluded the desensitization without symptoms. The remaining 7 children had mild adverse effects, mostly abdominal pain, throat pruritus, and gritty eyes, during the desensitization. Most reactions were transient and required no treatment. Antihistamines were given to only 1 patient to control symptoms. In patients who completed the protocol, the reactions invariably occurred with a dose greater than 32 mL. No adverse effects were observed in the control group.

DISCUSSION

There is currently no specific curative treatment available for IgE-mediated food allergy, for which total avoidance of the offending food is the only effective approach. It was previously suggested that CMA tends to disappear in older age in

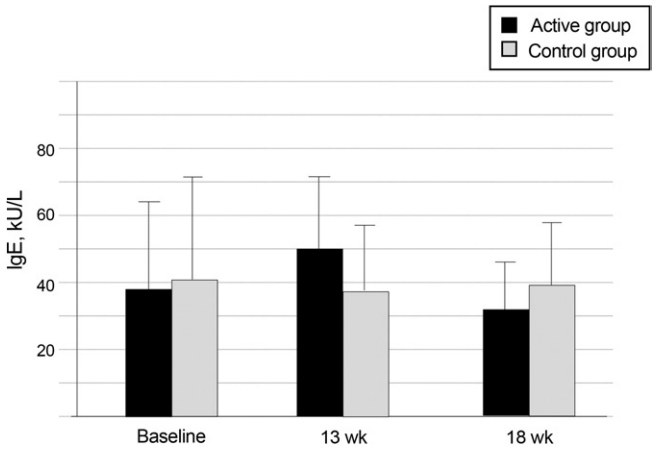

Figure 2. Mean cow's milk specific IgE levels at the 3 time points in active and control patients. No significant differences between and within groups were detected. Error bars represent SD.

most children and that approximately 85% of patients become tolerant by age 3 years. However, more recent studies[14,15] provided a less optimistic view. The burden of the disease and its tendency to persist across time in some individuals highlight the need for curative treatment, which can, in principle, reduce clinical symptoms and modify the natural history of the disease. In this regard, specific immunotherapy given by the oral route is regarded as a promising candidate.[16] Several attempts have been made to induce a tolerance to CM by administering progressively increasing doses of the food until intake of a full serving is achieved. These attempts have provided, overall, encouraging results, with an efficacy rate of 75% to 86%.[7,10,12,17] In a recent study[7] in children with severe CM-induced reactions, 36% became completely tolerant and 54% could ingest limited amounts of CM.

Currently, rush[18,19] and slow[7,11] protocols are used to achieve food tolerance. The first approach carries a certain risk of adverse events, and the second is, to some extent, impractical and time-consuming. In addition, part of the tolerance induction is conducted at home, without medical supervision,[7,11] and parents need to be carefully instructed on how to manage adverse reactions that can be also severe. The aim of the present study was to optimize the tolerance induction by identifying a more practical and patient-friendly approach. In this regard, weekly up-dosing oral immunotherapy seemed to be an acceptable compromise because it requires neither a complex protocol or hospitalization of the child. In fact, with the mentioned protocol, the dose increasing is performed every week at the clinic, and the patient is discharged within a few hours. In addition, the whole procedure lasts approximately 4 months, for a total of 28 visits. The study was designed as blinded and controlled, according to the requirements of evidence-based medicine. Soy milk cannot be strictly considered as a placebo, but in the case of CM, a "true" placebo is not available. In addition, it is true that patients can distinguish between soy milk and CM, but the procedure kept at least the investigator blinded. In such a study, the use of a control arm may be questionable because the absence of a reaction to control treatment (soy milk) was ascertained at the beginning of the study. On the other hand, a control arm was required to evaluate the occurrence, if any, of spontaneous tolerance development. In the control patients, no adverse effects occurred during the trial, but they maintained their sensitization to CM, as testified by the DBPCFC.

In this study, oral immunotherapy was effective: full specific tolerance was achieved in 10 of 13 actively treated children and partial tolerance in 1 of 13. In 2 patients, the desensitization had to be discontinued owing to severe adverse events. Therefore, the overall safety of the protocol is similar to that previously described.[7,18] The procedure is not devoid of adverse events, but the risk of having a reaction due to inadvertent ingestion is certainly higher than the risk of a reaction during a medically supervised desensitization. The results obtained in this study are, in addition, comparable in terms of clinical outcome with those reported in other studies[7,8,11,18,19] using daily protocols. Concerning immunologic outcomes, CM specific IgE levels remained unchanged overall. However, at the 8-mL dose, there was a transient increase in the IgE level, which returned to baseline levels when 200 mL of CM was reached. On the other hand, IgG4 levels against CM proteins exhibited a significant increase in the actively treated group. This is in agreement with the results described in other studies with milk[20] and peanuts[21] and is in line overall with the effects of specific immunotherapy for respiratory allergens. Also, in peanut allergy, it has been shown that oral desensitization induces down-regulation of the T_H2 response.[21] Thus, it can be speculated that the procedure described in the trial is a true immunotherapy inducing

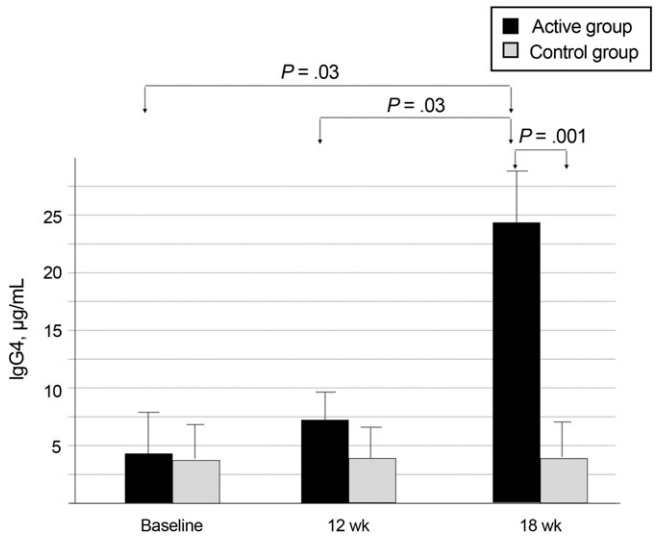

Figure 3. Mean cow's milk specific IgG4 levels at the 3 time points in the active and control patients. The significant intragroup and intergroup differences are shown at the top of the bars. Error bars represent SD.

immunologic changes. Whether the induced desensitization is permanent or transient is still unclear.[22] Staden and coworkers[11] reported that permanent tolerance could be achieved in 36% of patients with desensitized CMA. However, when children who achieved partial tolerance were included, efficacy increased to 64%. The latter group included patients who required a regular intake of CM to maintain tolerance or those who can tolerate lower-than-standard maximum doses.

In summary, these clinical data suggest that desensitization to CM can be successfully achieved in children with IgE-mediated food allergy. The proposed protocol is not time-consuming and is safe if performed in the hospital. It may represent a new therapeutic opportunity for children with IgE-mediated allergy to CM.

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