A new protocol for specific oral tolerance induction in children with IgE-mediated cow's milk allergy

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ABSTRACT

IgE-mediated cow's milk allergy (CMA) is a heavy burden for patients, particularly for children and their families. Allergen avoidance represents the only therapeutic option, but oral desensitization protocols have been suggested. Because of the long duration and complexity of these protocols we examined the feasibility of an oral tolerance induction protocol using a weekly up-dosing schedule. Children with IgE-mediated food allergy to milk, confirmed by a double-blind placebo-controlled food challenge, were recruited. Six of them were randomized to double-blind desensitization with milk or soy formula as placebo. Seven patients underwent the protocol in open fashion. The desensitization schedule started with one drop of whole CM diluted 1:25 every week. The dose was doubled weekly until the 18th week to achieve an intake of 200 mL in ~4 months. Of the 13 children enrolled, 10 children received CM and 3 control children received soy formula. Full tolerance (200 mL of milk) was achieved in 7 children; in 2 children this therapeutic approach failed, because severe reactions occurred during the procedure. One patient achieved a partial tolerance (64 mL of milk). The three control children receiving placebo still showed a positive food challenge at the end of the study. A weekly up-dosing oral tolerance induction could be a viable alternative to traditional protocols for children with IgE-mediated CMA.

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Key words: Cow's milk allergy, desensitization, food allergy, food challenge, IgE, oral immunotherapy, oral tolerance induction, protocol, up-dosing, weekly schedule

Adverse reactions to foods, which include IgE-mediated allergy, have been reported to occur in up to 25% of the general population. However, when food challenges are performed, the diagnosis is confirmed only in a small proportion of patients.[1] The highest prevalence of food allergy is observed during infancy and early childhood.[2] In children, cow's milk allergy (CMA) is one of the most common food allergies,[3] and it is of special relevance due to the nutritional implications. The management of food allergy is still essentially based on patients' (and parents') education on avoidance of the suspected allergen(s) and on recognizing the importance of detecting early symptoms of an allergic reaction as in the case of accidental ingestion and progressing to appropriate emergency therapy thereafter. Provided that the diagnosis of food allergy is accurate, allergen avoidance is currently the only causal therapeutic option. Nonetheless, in the case of CMA, allergen avoidance implies the deprivation of essential nutrients and their replacement with substitute formulas (e.g., soy formulas or hydrolyzed milks), which may add additional unpleasant adverse effects or have an incomplete nutritional content. Moreover, even when appropriate education is provided, the risk of severe life-threatening allergic reactions due to inadvertent ingestion or hidden allergens remains real. In general, it has been shown that infants with non–IgE-mediated CMA have a high recovery rate compared with infants with high IgE levels to CM proteins (IgE-mediated CMA).[4–6] In addition, those with IgE-mediated CMA are at greater risk of developing other food allergies, asthma, and rhinoconjunctivitis.

Based on these considerations, allergen-specific immunotherapy has been repeatedly proposed as a therapeutic strategy.[7–10] In the case of CMA, the oral exposure to increasing doses of the food is preferably termed as specific oral tolerance induction (SOTI), because its mechanisms of action partly differ from those of specific immunotherapy to inhalant or hymenoptera allergens. In fact, although desensitization is food specific, the tolerance is frequently lost if the food is not regularly introduced.[4] Studies in animal models have shown that either anergy induction or activation of regulatory T cells may occur with oral desensitization,[11,12] but there are few similar studies in humans. Although both an increase of specific IgG4 and a decrease of specific IgE have also been reported,[13,14] these

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Table 1 **Demographic data of patients at baseline**

	Oral Desensitization	Placebo
No.	10	3
Sex: Male/female	6/4	2/1
Mean age (yr)	8	8
Age range (yr)	5–10	6–10
Duration of food allergy to cow's milk, mean ± SD (yr)	7.8 ± 1.9	7.9 ± 1.5
Milk-specific IgE, mean ± SD (kU/L)	38.1 ± 7.3	30.5 ± 4.0
Other food allergy	None	None
Allergy to inhalant allergens (*n*, %)	2 (20%)	—

changes in antibody production might represent epiphenomena that do not reflect the true primary pathogenetic mechanisms of SOTI.

Currently, oral desensitization to CM is performed starting with very low quantities, which are then slowly increased up to an amount comparable with the usual daily intake. Afterward, the food is given daily in a maintenance dosage to maintain the tolerant state. The schedules of administration are usually of long duration[7,14] or require hospitalization of the allergic children.[10] Thus, we evaluated the feasibility and the effectiveness of a weekly up-dosing schedule for desensitization, which is more patient friendly and easier to perform.

METHODS

We evaluated the efficacy of a weekly up-dosing SOTI in a group of children (Table 1) with severe IgE-mediated CMA allergy, over a 4-month period. The target was to enable children to tolerate at least 200 mL of CM or, alternatively, to identify the maximum tolerated amount of CM. The inner Ethical Committee approved the randomized double blind, placebo-controlled design for six patients only. In these patients a soy formula was used as placebo. Seven additional patients underwent desensitization in an open fashion.

Patients and Diagnosis

Children of both sexes aged 5–10 years, with ascertained IgE-mediated CMA, were enrolled at the Department of Pediatrics, Allergy Unit, Messina University Hospital. The diagnosis of CMA was based on clinical history, demonstration of CM-specific IgE, and confirmed by the double-blind placebo-controlled food challenge (DBPCFC). No children had to have positive history of allergic reactions to soy formula or positive skin test or serum-specific IgE to soy, to assure safety in the use of soy formula in the DBPCFC. Sensitizations to other foods represented exclusion criteria as well.

Skin tests were performed on the volar forearm surface, either with commercial extracts and with the prick-by-prick technique. In this latter procedure, undiluted fresh CM and soy formula were used. A wheal of ≥3 mm was considered positive, according to recommendations. The DBPCFC was performed at the clinic, under medical supervision and with full facilities for resuscitation available. Fresh CM or soy formula (Humana Sinelac, Milan, Italy) as placebo was administered at increasing doses of 0.1, 0.3, 1.0, 3.0, 10.0, 30.0, and 100 mL in a double-blind manner. The time interval between doses was 20 minutes. The challenge procedure was stopped when clinical symptoms appeared or when the highest dose was reached[15] (Table 2). After completing, the DBPCFC children were kept under observation for at least 6 hours and then discharged. Food challenges were scored as positive by a pediatric allergist if a single symptom or any of the following objective clinical reactions was observed: urticaria, angioedema, wheezing, rhinitis, vomiting, diarrhea, protracted abdominal pain, exacerbation of atopic dermatitis, or shock. The DBPCFC was repeated every year in those patients in whom the SOTI procedure was not successful to determine a possible spontaneous resolution of IgE-mediated CMA.

Desensitization Protocol

The desensitization consisted of administration of increasing amounts of CM at weekly intervals, starting with one drop of whole milk, diluted 1:25. The dose was doubled every week, until the 18th week, to achieve a total intake of 200 mL in ~4 months. No ingestion of CM was allowed out of the scheduled protocol, and oral antihistamines were not given to the patients during the up-dosing period. When an intercurrent illness intervened (common cold and/or fever) during the oral desensitization(s) the dose of milk was not increased, and the last dose was repeated. All doses were administered at the clinic under medical supervision. After receiving the dose, children were carefully assessed and considered to have a positive reaction when one or more of the following symptoms appeared: urticaria, exacerbation of eczema (at least 10 points increase in Scorad index), angioedema and/or generalized urticaria, vomiting, diarrhea, rhinitis, se-

Table 2 **Age of onset of cow's milk allergy, specific IgE, skin-prick tests, related symptoms, and results of double-blind placebo-controlled food challenge (DBPCFC) before the beginning of oral desensitization**

Patient No.	Age at Onset (mo)	Specific IgE (kU/L)	Skin Test (mm)	Symptoms	Symptoms at DBPCFC	CM-Eliciting Symptoms (cumulative, in mL)
1	5	40.3	12	Anaphylaxis	Not done	—
2	4	37.7	12	Severe atopic dermatitis, urticaria	Pruritus, generalized urticaria	0.4
3	6	45.4	10	Anaphylaxis	Not done	—
4	3	39.0	6	Severe atopic dermatitis	Pruritus, abdominal pain, sneezing	14.4
5	6	35.7	9	Urticaria, angioedema, asthma	Pruritus, erythema, cough asthma	4.4
6	7	28.5	7	Urticaria, abdominal pain, vomiting	Urticaria, abdominal pain, diarrhea	14.4
7	5	33.9	5	Moderate atopic dermatitis, urticaria, angioedema	Pruritus, erythema, generalized urticaria	4.4
8	4	36.3	9	Angioedema, urticaria, rhinitis	Urticaria, sneezing, cough	0.4
9	7	38.6	8	Angioedema, cough, wheezing	Pruritus, angioedema	1.4
10	8	26.5	6	Abdominal pain, diarrhea urticaria	Urticaria, vomiting, diarrhea	4.4
11	6	39.8	7	Severe atopic dermatitis	Pruritus, erythema, angioedema	44.4
12	6	42.9	8	Urticaria, angioedema, moderate atopic dermatitis	Erythema, atopic dermatitis, urticaria	1.4
13	4	40.1	6	Urticaria, angioedema	Pruritus, angioedema	4.4

vere conjunctivitis, or anaphylactic reaction. If symptoms were judged mild, such as abdominal pain, erythema, throat pruritus, and gritty eyes, no action was taken and the protocol was continued. On the other hand, when moderate and/or serious symptoms appeared, appropriate medical treatment was given and the SOTI procedure was interrupted.

RESULTS

Thirteen children (age range, 5–10 years; mean age, 8 years; 8 boys) were enrolled for the study. Six of them were randomized to a double-blind placebo-controlled phase, and seven children underwent the SOTI procedure in a open fashion. Their demographic and clinical characteristics are shown in Table 1. All but two children underwent the DBPCFC before starting oral desensitization. The results of the DBPCFC are reported in Table 2. The two patients with a clear history to anaphylaxis to CM were not challenged because of the risk of serious side effects. Of note, in one of those patients the smell or contact with the CM caused sneezing, erythema, and angioedema, and the other child developed urticaria, angioedema, and asthma after ingestion of hidden CM in a cake.

In the double-blind group, patient No. 10 of Table 3, with 4 mL of CM, had urticaria, rhinitis, throat pruritus, vomiting, and circulatory collapse. He was treated with intramuscular adrenaline and antihistamines and i.v. corticosteroids and gradually recovered. The desensitization was stopped and he is currently on total avoidance of CM and hidden milk proteins. The other two children completed the procedure and tolerated the maximum dose of 200 mL without problems. The three placebo patients had no symptoms during the protocol, but they remained positive at the DBPCFC performed at the end of the study. In the open study group (seven patients), five children reached the dose of 200 mL of CM and tolerated well the desensitization protocol. One patient achieved a partial tolerance, because with the dose of 64 mL she developed urticaria, angioedema, and cough, needing intramuscular antihistamines and corticosteroids. In this case, the desen-

Table 3 **Summary of the results during specific oral tolerance induction with cow's milk (CM)***

Patient	Age at the Desensitization	Symptoms during CM Desensitization	Dose of CM-Eliciting Symptoms (mL)	Action Taken	Outcome of CM Desensitization
1	10 yr 3 mo	Rhinitis, cough, asthma, generalized urticaria	2	Adrenaline, steroids, antihistamines, salbutamol, protocol stopped	Desensitization failed
2	9 yr 2 mo	Abdominal pain, throat pruritus	128	Antihistamine, steroid.	Tolerated 200 mL of whole CM
3	5 yr 9 mo	Generalized urticaria, angioedema, cough	64	Antihistamines, steroids, desensitization stopped	Tolerated a lower dosage of the CM than the full dosage
4*	7 yr 1 mo	Throat pruritus, gritty eyes	32	None	Tolerated 200 mL of whole CM
5	6 yr 4 mo	Abdominal pain, gritty eyes, watery eyes	128	None	Tolerated 200 mL of whole CM
6	9 yr 5 mo	Transient erythema (face and hands)	128	None	Tolerated 200 mL of whole CM
7*	10 yr 1 mo	—	—	—	Tolerated 200 mL of whole CM
8	6 yr 3 mo	Abdominal pain, gritty eyes	64	None	Tolerated 200 mL of whole CM
9	5 yr 4 mo	—	—	—	Tolerated 200 mL of whole CM
10*	8 yr 4 mo	Rhinitis, urticaria, cough, hypotension, dyspnea	4	Adrenaline, steroids, salbutamol, antihistamine, protocol stopped	Desensitization failed

The patients (no. 3) treated with soy milk as placebo had no symptoms during specific oral tolerance induction.
**Patients 4, 7, and 10 underwent double-blind desensitization; others had specific oral tolerance induction in open fashion.*

sitization was stopped. Currently, she can eat "hidden CM," cakes, snacks, delicatessen ice-creams, and moderate amounts of CM without symptoms. Finally, one patient failed to achieve tolerance, because 4 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. The clinical results of the desensitization with CM are summarized in Table 3.

DISCUSSION

The treatment of children with IgE-mediated food allergy is still a matter of controversy, and the only approach of proven efficacy is complete allergen avoidance. Despite this, it is now clear that the prognosis, in term of resolution of the IgE-mediated CMA, appears significantly worse than what was previously reported[16] and the high rate of resolution over time has been questioned.[6] Thus, the alternative option of an active treatment would be desirable, and specific immunotherapy or oral tolerance induction has been proposed as a good candidate.[17]

Preliminary studies on oral tolerance induction have shown promising results with efficacy rates between 75 and 86%.[7,14,18,19] In a recent study in children with severe CM-induced reactions, 36% became completely tolerant and 54% could ingest limited amounts of milk.[10]

Currently, long-lasting protocols[7,20] or rush protocols[21,22] have been used to achieve food tolerance. Other methods such as sublingual immunotherapy using the spit-out methods or low doses of CM[8–23] could be further options. A weekly up-dosing desensitization

is more easy to do and does not require a complex protocol, with serial dilutions and drop-by-drop increasing of the doses. Indeed, the results achieved in our study are comparable in terms of clinical outcome and failures to other studies using long protocols. Thus, the weekly up-dosing can be proposed as a useful alternative to achieve a desensitizations.

Whether the induced tolerance is permanent or transient is still unclear.[24] Staden and coworkers reported that a permanent tolerance could be achieved in 36% of desensitized CM patients.[20] However, when children who achieved partial tolerance were included, the efficacy rate raised to 64%. This group included patients who required a regular intake of CM to maintain tolerance or those who can tolerate a dosage lower than the standard maximum dose. It is clear that in the case of food allergy to milk or eggs, the maintenance of desensitization is easy to do because those foods are part of the normal diet of children and adults and are largely used in both European and American cuisine.

Currently, one double-blind placebo-controlled study is available in children with CMA. For the first time immunologic tests were performed and the authors have found that milk IgG levels increased significantly in the active treatment group, with a predominant milk IgG4 level increase.[25] In the double-blind placebo-controlled part of the our study two of three children treated with the CM protocol achieved full tolerance to milk. The children receiving soy formula had no symptoms during the desensitization course; however, the DBPCFC with CM at the end of the trial showed that no tolerance had been achieved. As a consequence, in the case of food allergy, the use of a placebo arm seems to be particularly useful either to control immunologic changes or to assess the mechanisms of CM desensitization.

Our clinical data suggest that SOTI to CM may be achieved in children with IgE-mediated food allergy. The procedure is not devoid of severe 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. Our protocol is not time-consuming and it is quite safe if performed in the hospital. This approach is similar to allergen immunotherapy performed with inhalant allergens.[26,27] However, in two patients (20%) this therapeutical approach failed. It can be speculated that in these patients a "long-lasting daily" SOTI[7,20] would be preferable to achieve the tolerance. In summary, the current encouraging results represent a new therapeutic opportunity,[28,29] particularly for children (and their families) with persistent food allergy, who would deserve better than strict allergen avoidance.[30]

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