

Specific oral tolerance induction in children with very severe cow's milk-induced reactions

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Background: Some children allergic to cow's milk proteins (CMPs) experience exceptionally severe reactions after ingesting only trace amounts of antigen. Avoiding the food and carrying self-injectable epinephrine are the current strategies for their management.

Objective: The aim of this study was to evaluate the safety and efficacy of specific oral tolerance induction (SOTI) for children with severe CMP-induced systemic reactions.

Methods: Ninety-seven children aged 5 years or older with a history of severe allergic reactions and very high CMP-specific IgE levels were selected for a double-blind, placebo-controlled food challenge. Sixty had positive test results to very small amounts of milk and were randomly divided in 2 different groups. Thirty children (group A) immediately began SOTI, whereas the remaining 30 (group B) were kept on a milk-free diet and followed for 1 year.

Results: After 1 year, 11 (36%) of 30 children in group A had become completely tolerant, 16 (54%) could take limited amounts of milk (5-150 mL), and 3 (10%) were not able to complete the protocol because of persistent respiratory or abdominal complaints. In group B the result of the double-blind, placebo-controlled food challenge performed after a year was positive in all 30 cases ($P < .001$).

Conclusions: In this study SOTI was effective in a significant percentage of cases.

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Key words: Cow's milk allergy, severe reactions, children, specific oral tolerance induction

Food allergy is the primary cause of anaphylaxis in children, and in Europe cow's milk proteins (CMPs) and hen's egg proteins are the main offenders.¹⁻⁴ Limited published evidence shows that specific oral tolerance induction (SOTI) is a possible intervention.⁵⁻¹¹ Children with very severe cow's milk allergy are typically excluded from these studies, and no study has ever specifically attempted SOTI with children who have very severe allergy to CMPs. Commonly, such children show very high levels of specific IgE¹² and have severe reactions after the ingestion of,

Abbreviations used

CMP: Cow's milk protein

DBPCFC: Double-blind, placebo-controlled food challenge

SOTI: Specific oral tolerance induction

inhalation of, or even skin contact with trace amounts of antigen.¹³⁻¹⁷ For them, the risk of fatal reactions is real and increases with age as a result of reduced parental control over their diet.¹⁸ The possibility of spontaneous recovery is quite rare in patients 6 years or older with very high levels of specific IgE.¹⁹⁻²² Currently, standard management for these subjects consists of strict antigen avoidance combined with instructions for recognizing symptoms, prescription for self-injectable epinephrine for emergency use, and information on access to emergency services.² This approach has a negative effect on the child's behavior and compromises the quality of life of the entire family because of the fear of unexpected or life-threatening reactions.²³ Indeed, it is difficult to avoid completely a common food, and the likelihood of unintended exposure is considerable.^{18,24,25} Epinephrine is life-saving, but it might not be available or administered soon enough.^{18,24-26} For all these reasons, we investigated the efficacy of SOTI for children with severe milk allergy by using an original protocol consisting of an initial in-hospital phase, followed by a slow dose increase at home.

METHODS

Enrollment of patients and inclusion criteria

The population eligible for our study included children aged 5 to 17 years with milk-specific IgE levels (CAP System; Pharmacia & Upjohn AB Diagnostics, Uppsala, Sweden) of greater than 85 kUA/L and a positive history for at least 1 severe allergic reaction (ie, reactions defined as class 4 and 5 according to Clark's classification²⁷; Table I) after accidental exposure to milk or dairy products requiring emergency treatment.

Using these inclusion criteria, we selected 97 patients seen between January 2003 and December 2005 at the Paediatric Department for Allergy and Asthma of the "Burlo Garofolo Children's Hospital" in Trieste. All subjects underwent a double-blind, placebo-controlled food challenge (DBPCFC), starting with very low amounts of diluted milk, to reduce the risks related to this procedure.²⁸ The DBPCFC started with 1 drop of a solution made of 1 part cow's milk and 9 parts of an amino acid-based infant formula modified with vanilla flavor. We then administered 5 drops of the same solution (corresponding to about 0.025 mL of whole milk) and continued by doubling the amount every 20 minutes: 5 drops, 10 drops, 1 mL, 2 mL, 4 mL, 8 mL, and so on. The placebo was the amino acid-based infant formula alone with the same vanilla flavor. Children were considered eligible only if they had symptoms during the DBPCFC to the lowest doses (up to 8 mL of diluted formula and corresponding 0.8 mL of whole milk).

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TABLE I. Severity grading of reaction according to Clark and Ewan²⁷

Reaction grade	Clinical features
1. Mild	Localized cutaneous erythema/urticaria/angioedema/oral pruritus
2. Mild	Generalized erythema/urticaria/angioedema
3. Mild	At least 1 or 2 plus gastrointestinal symptoms/rhinoconjunctivitis
4. Moderate	Mild laryngeal edema (voice change/tightening of throat)/mild asthma
5. Severe	Marked dyspnea/hypotensive symptoms (collapse/loss of consciousness)

/, And/or.

The children enrolled were randomized in 2 groups: A and B. A simple computerized randomization was performed; blinding was ensured by using sequentially numbered, opaque, sealed envelopes. Group A started the SOTI immediately after the DBPCFC. Group B maintained a milk-free diet for 1 year and then underwent another DBPCFC. The characteristics of the enrolled children are shown in Table II.

Exclusion criteria

Parents with a history of unreliable management of complications and treatments, limited availability to emergency facilities in the area where the family lived, and children with poorly controlled asthma were all considered to be exclusion criteria.

Specific IgE detection

Specific IgE levels in serum samples were measured by using the Phadea CAP System FEIA (Phadea, formerly Pharmacia & Upjohn AB Diagnostics) for whole milk and the major CMP (casein, β -lactoglobulin, and α -lactalbumin) at the time of enrollment and after 6 and 12 months. Skin prick tests were performed with fresh whole milk, along with negative (saline) and positive (histamine) controls.

Consensus and ethics committee approval

Informed consent was obtained from all parents. The ethics committee of the I.R.C.C.S. Burlo Garofolo, Trieste, approved the study.

SOTI protocol

The SOTI process consisted of 2 phases. The first phase took place in the hospital, with a rapid increase in milk dosage (rush phase, Table III). The children were admitted for 10 days and were dosed daily, as shown in Table III (first day: 6 doses of diluted milk at 1-hour intervals; second, third, and fourth day: 4 doses of diluted milk at 2-hour intervals; and then 3 daily doses at 2-hour intervals, increasing the concentration of the solution each day to reach whole milk). During hospital admission, all children were administered antihistamine daily (oxatamide, 1 mg/kg per day), all had a venous line placed, and a complete emergency kit was always available. A protocol for adverse event treatment was established with partial modification of the standard international guidelines²⁹ to include nebulized epinephrine³⁰ (1 mg/10 kg; maximum, 3 mg of epinephrine 1:1000 diluted in 3 mL of saline solution) for early treatment of mild-to-moderate respiratory symptoms.

The children were discharged after 10 days. At home, the subjects followed a slow increasing phase (increasing by 1 mL every second day), personalized for each subject, on the basis of the frequency and severity of side effects and the confidence of the parents. Parents were provided with written instructions for the gradual increase in milk dose at home. Appropriate training to manage adverse reactions, including the use of nebulized and self-injectable

TABLE II. Demographic data, RAST for cow's milk, skin prick test with whole cow's milk, and threshold of reactivity in the DBPCFC for groups A (treatment group) and B (control group)

Characteristics	Group A (SOTI)	Group B
No.	30	30
Mean age (y; range)	7.9 (5-17)	8.1 (5-16)
Female sex	9 (30%)	12 (40%)
RAST >100 kUA/L	23	24
RAST 85-100 kUA/L	7	6
Mean wheal diameter of skin prick test (mm; range)	11.9 (7-24)	11.3 (7-20)
DBPCFC (threshold of reactivity)		
≤3° dose*	6	3
4°-6° dose†	24	27

*Whole milk, <0.1 mL.

†Whole milk, 0.2 to 0.8 mL.

TABLE III. In-hospital treatment schedule: Rush phase

Day	Dilution	Doses
1	1 drop of CM in 10 mL of water	5 drops, 10 drops, 1 mL, 2 mL, 5 mL, 10 mL
2	5 drops of CM in 20 mL of water	2 mL, 4 mL, 8 mL, 16 mL
3	1 mL of CM in 20 mL of water	2 mL, 4 mL, 8 mL, 12 mL
4	3 mL of CM in 20 mL of water	3 mL, 6 mL, 9 mL, 10 mL
5	10 mL of CM in 20 mL of water (1:3)	3 mL, 6 mL, 9 mL
6	10 mL of CM in 10 mL of water (1:2)	3 mL, 6 mL, 9 mL
7	No dilution: pure CM (1:1)	2 mL, 4 mL, 6 mL
8	No dilution: pure CM (1:1)	4 mL, 7 mL, 10 mL
9	No dilution: pure CM (1:1)	8 mL, 12 mL, 15 mL
10	No dilution: pure CM (1:1)	13 mL, 16 mL, 20 mL

Doses were administered at 1-hour intervals on the first day and at 2-hour intervals on subsequent days (from the second to the 10th day).

CM, Cow's milk.

epinephrine, was provided along with a dedicated telephone number available 24 hours a day. Each family in both groups was contacted by means of telephone periodically. Once home dosing reached 150 mL of whole milk in a single dose, the patients were asked to eat increasing amounts of dairy products (eg, yogurt, cheeses, cottage cheese, mozzarella, parmesan cheese, and ice cream). We recommended abstention from exercise for 3 hours after milk intake to minimize the risk of food/exercise-induced anaphylaxis.³¹ Antihistamine treatment was continued at home until the 150-mL single dose was reached and then reduced over 4 weeks. Subjects were discontinued from the study because of adverse reactions if they were severe (class 5, Table I) or frequent despite decreasing dosage. The SOTI was considered to have failed if the child did not reach at least 5 mL of undiluted milk in a single dose after 1 year or if participation was stopped for adverse effects.

Outcome measures

Both groups were evaluated for the following: (1) the number of children that could tolerate 150 mL of cow's milk or more in a single dose (maximum tolerance); (2) the number of children able to drink at least 5 mL but less than 150 mL in a single dose (partial tolerance); and (3) the number of adverse events experienced during the study period recorded in terms of severity and treatment required.

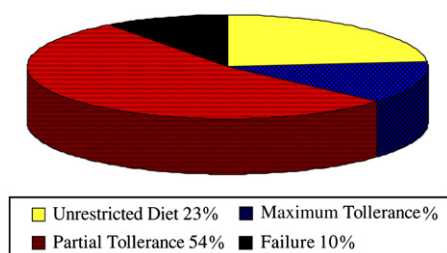


FIG 1. Outcome at 1 year in treatment group A. Unrestricted diet: Patients who could tolerate unlimited amount of cow's milk and dairy products. Large tolerance: Patients who could tolerate at least 150 mL of cow's milk daily. Partial tolerance: Patients who could tolerate a limited amount (5-150 mL) of cow's milk daily. Failure: Patients who stopped the protocol and restarted an avoidance diet.

Sample size calculation

Given the limited data available in the literature about SOTI, the sample size calculation was carried out based on the main outcome of our study (ie, maximum oral tolerance), the natural evolution of food allergy, and our own experience in this field. Assuming a complete success after 1 year in 35% of subjects treated with SOTI versus a spontaneous recovery in 5% of control subjects, 60 subjects (30 in each group) were required for a power of 80% and an α error of .05.

Statistical analysis

Categorical data are presented as numbers and percentages. The percentage of cow's milk-tolerant patients at the end of the follow-up in each group was compared by using the χ^2 test. A *P* value of less than .05 was considered significant for all comparisons.

RESULTS

Seventy-two of 97 children tested were selected for participation because they presented symptoms at the DBPCFC for doses of 0.8 mL or less of cow's milk. Twelve of 72 were not eligible because they met 1 or more exclusion criteria (5 cases) or because the parents rejected the procedure (7 children). Thirty children were enrolled in each group. The 2 study groups, A and B (the treatment and control groups, respectively) were homogeneous for age, sex, clinical symptoms, skin prick test results, specific IgE levels, and DBPCFC outcome (threshold of reactivity). The clinical and laboratory data of the 60 enrolled children are shown in Table II. At the end of the in-hospital phase, 9 subjects in group A had reached the single dose of 20 mL of whole milk, as established by the protocol (Table III). The remainder of group A was stabilized at lower doses because of frequent allergic reactions that required attenuation or interruption of the SOTI schedule.

After 1 year, 11 (36%) of 30 subjects achieved a daily intake of cow's milk equal to 150 mL or more, many of them with the addition of different dairy products, enough to permit an unrestricted diet. Sixteen (54%) subjects were able to take a limited amount of milk, ranging from 5 to 150 mL, and 3 (10%) children were not able to continue in the study because of allergic symptoms characterized by respiratory or abdominal complaints (Fig 1).

For these children, we observed them, in an open feeding, ingest the amount of milk they consumed as their daily treatment dose, confirming no symptoms. Children of group B (control group) underwent a second DBPCFC, the result of which was again positive in all 30 cases for minimal amounts of milk,

TABLE IV. Group A: Symptoms and treatment required during SOTI in the hospital (10 days) and at home (1 year)

Symptoms	No. of in-hospital patients (total no. of reactions)	No. of at-home patients (total no. of reactions)
Lip or mouth pruritus	30 (355)	14 (85)
Perioral urticaria	28 (37)	17 (22)
Erythema or generalized urticaria	14 (17)	7 (13)
Abdominal pain with or without vomiting	23 (47)	14 (32)
Rhinoconjunctivitis	18 (23)	3 (8)
Mild laryngospasm	14 (15)	3 (5)
Mild bronchospasm	12 (28)	8 (19)

Administered treatment	No. of in-hospital patients (total no. of administered treatments)	No. of at-home patients (total no. of administered treatments)
Oral steroids	8 (16)	17 (35)
Nebulized epinephrine	18 (22)	6 (9)
Intramuscular epinephrine	4 (4)	1 (1)

demonstrating that there had been no spontaneous improvement. In particular, 1 child reached 2 mL of whole milk and 2 children reached 1 mL, but none could tolerate 5 mL (partial tolerance), and most displayed the same reactions to the very first doses of diluted milk as observed the year before.

The difference between the 2 groups is statistically significant ($P < .001$) when considering group A children who achieved complete tolerance (11/30 vs 0/30) and group A children who achieved partial tolerance (27/30 vs 0/30).

Adverse reactions were common in all group A participants. Almost all children presented with 1 or more allergic symptoms, mainly cutaneous (urticaria and angioedema) or abdominal (Table IV). Notably, all symptoms occurred from a few minutes to 2 hours after milk ingestion. No child had class 5 reactions.

During hospitalization (the rush phase), intramuscular epinephrine was administered 4 times in 4 children, whereas nebulized epinephrine was used in 18 children and more than once in 7 children because of recurring respiratory symptoms.

During the home dosing, 2 children required treatment in the emergency department. They were initially treated by their parents in accordance with the protocol for adverse event treatment and then received further treatment in the hospital with oral steroids, antihistamine, and intramuscular epinephrine (1 case).

In group B 6 (20%) children had adverse reactions caused by accidental exposure to milk during the study period. These reactions were all mild, one caused by ingestion and the others caused by skin contact.

To simplify data presentation, we report only the specific IgE value for whole milk because no correlation was found between the SOTI outcome and the single CMP (casein, β -lactoglobulin, and α -lactalbumin)-specific IgE levels.

Specific IgE measured at 6 and 12 months showed a significant decrease after SOTI in 15 of 30 subjects (Fig 2). It is possible that the cutoff point of 100 kUA/L precluded detecting specific IgE reduction in other subjects.

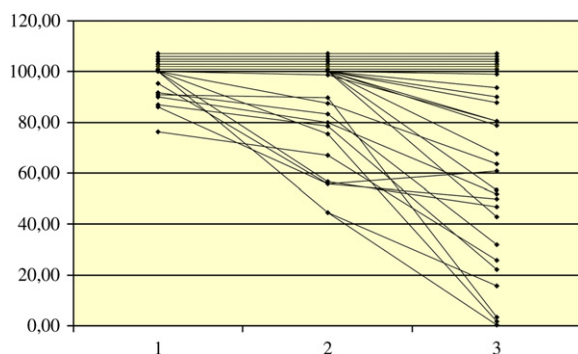


FIG 2. Group A. Trend of cow's milk-specific IgE values before starting desensitization (1) and after 6 (2) and 12 (3) months of follow-up. A 101 kUA/L value was assigned to all values of greater than 100 kUA/L (the highest limit of detection of this technique). Clear reduction has been found in 15 patients.

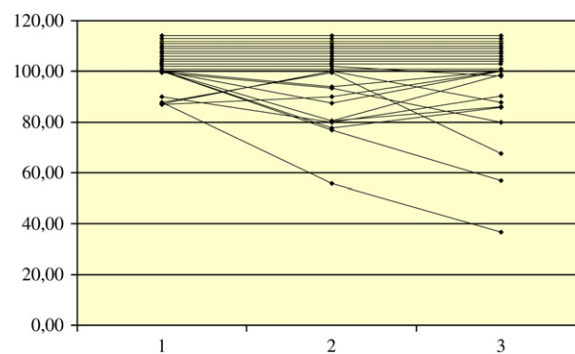


FIG 3. Group B. Trend of cow's milk-specific IgE values at the time of DBPCFC (1) and after 6 (2) and 12 (3) months. A 101 kUA/L value was assigned to all values of greater than 100 kUA/L (the highest limit of detection of this technique). No significant change has been found, except for a slight reduction in 3 cases and an increase in 1 case.

In group B IgE levels after 1 year were essentially unchanged, with a slight reduction in 3 subjects and an increase in 1 other subject (Fig 3).

DISCUSSION

Our study shows for the first time that SOTI can be achieved in patients affected by severe food allergy. These subjects represent a serious clinical problem because of the constant risk of severe and possibly fatal reactions avoidable only through a restrictive diet that has a negative effect on the quality of life of both the child and his or her family. Because milk is such a common contaminant in foods, it has been estimated that there is a 75% likelihood of accidental exposure to the offending food over a 5-year period among patients practicing an antigen-free diet.²⁴ Epinephrine is lifesaving, but it is not always available in time^{18,25} or is not always efficacious.²⁴

Limited evidence in the literature suggests that SOTI can be effective,^{5-11,32} but there have been no reports that include such a high number of patients with very high specific IgE levels and a history of severe reactions to even minor exposure to milk.

Our primary concern while developing the study was to minimize the risk of life-threatening events caused by SOTI. As part of our effort to make the procedure as safe as possible, the DBPCFC began with very low doses of diluted cow's milk, and the SOTI started in the hospital to reach fairly significant amounts of milk intake (the rush phase) under medical supervision.

In this study 36% of the treated children were able to ingest cow's milk and dairy products after 1 year without any restrictions, as opposed to none in the control group ($P < .001$).

Although more than 50% of group A children did not reach the end result of an unrestricted diet, they were able to ingest considerably higher amounts of cow's milk than the control group. This result is important because the danger associated with accidental exposure to small amounts of cow's milk is significantly reduced.

The total number of reactions during the study was high both in the hospital and at home (table IV). No patient required intravenous fluids, intravenous epinephrine, resuscitation, or intubation.

In most cases parents chose to continue the administration of cow's milk in spite of frequent symptoms, even when the milk dose could not be increased. Our data are still too limited to

estimate the true risk of fatal or near-fatal events in these subjects, and far more research is needed to confirm the safety of this approach.

SOTI in children with severe milk allergy is no magic bullet and in a sense resembles a tightrope-balancing act. Nevertheless, we believe that the more severe the food allergy is and the more common the implicated food, the better the cost/benefit ratio.

During the course of the study, all the parents were highly motivated because of their awareness of the child's problem and of the very poor quality of life deriving from antigen avoidance. The parents of treated children expressed great satisfaction, including those whose children had experienced major symptoms and achieved only partial success.

No child in group B spontaneously acquired tolerance during the year of observation; however, this period of time is too short to state confidently that spontaneous resolution rarely occurs. It has been shown in the literature that older children have a decreased chance of spontaneously achieving tolerance.³³ Therefore our intervention seems justified, despite the high frequency and severity of allergic reactions.

In addition to the risks related to SOTI, the commitment that such a protocol requires of the entire family is significant. An appropriate level of commitment is also required from the medical team. The simple availability of 24-hour telephone contact turned out to be crucial in supporting and counseling the parents who followed the home schedule; however, this requires full cooperation by study doctors. For these reasons, both highly motivated parents and highly committed medical staff are mandatory.

The immunologic mechanisms underlying SOTI are still unclear. It is not known whether this is a true, long-lasting immunity shift (no longer T_H2 oriented³⁴) or whether tolerance is obtained through temporary reduction of specific IgE levels, as happens in desensitization to antibiotics.³⁵ In the latter case tolerance disappears when exposure to the antigen is suspended for any reason, as previously reported in other cases of SOTI after short-term treatment,¹¹ although in one case it has been reported to persist after long-term treatment.³² This is a relevant issue because it affects the long-term-effects of the treatment. We recommend to our patients a constant intake of milk in the years after SOTI to promote the decrease of specific IgE levels and to reduce the risk of recurrence of the symptoms if intake of milk is discontinued.¹¹ The hypothesis is that oral tolerance is first achieved

through an antigen-specific mast cell desensitization, followed by a T_H -mediated process with normalization of IgE levels. Data on past patients who underwent the same SOTI protocol before 2003 show a constant decrease in IgE levels over the years with continuous milk consumption (data available on request).

Nevertheless, it must be emphasized that this is a working hypothesis, and the preliminary evidence reported here requires further long-term study.

In conclusion, this study confirms that tolerance can be achieved through a progressive increase of oral administration of cow's milk in a significant percentage of children with severe CMP allergy. Allergic symptoms were common during the increasing dosage phase, but symptoms typically were managed effectively by educated parents. Even a partial tolerance (ie, ingestion of limited amounts of cow milk) resulted in a striking improvement in quality of life. The risk of fatal anaphylaxis during SOTI compared with the risk of fatal anaphylaxis after accidental exposure in untreated patients still needs to be determined on the basis of larger numbers of patients and longer follow-up periods. Therefore despite these encouraging results, SOTI should be restricted to carefully selected clinical contexts.

Clinical implications: Tolerance can be achieved through a progressive increase in oral administration of cow's milk. This procedure should be conducted in highly controlled settings.

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