



Efficacy and safety of oral desensitization in children with cow's milk allergy according to their serum specific IgE level

Carmen García-Ara, MD, PhD; María Pedrosa, MD; María Teresa Belver, MD; María Flor Martín-Muñoz, MD, PhD; Santiago Quirce, MD, PhD; and Teresa Boyano-Martínez, MD

Department of Allergy, Hospital La Paz Institute for Health Research (IdiPAZ), Madrid, Spain

ARTICLE INFO

Article history:

Received for publication November 9, 2012.

Received in revised form January 11, 2013.

Accepted for publication January 17, 2013.

ABSTRACT

Background: Oral desensitization in children allergic to cow's milk proteins is not risk free. The analysis of factors that may influence the outcome is of utmost importance.

Objective: To analyze the efficacy and safety of the oral desensitization according to specific IgE (sIgE) level and adverse events during the maintenance phase.

Methods: Thirty-six patients allergic to cow's milk (mean age, 7 years) were included in an oral desensitization protocol. Patients were grouped according to sIgE levels (ImmunoCAP) into groups 1 (sIgE <3.5 kU/L), 2 (3.5–17 kU/L), and 3 (>17–50 kU/L). Nineteen children were included as a control group. Serum sIgE levels to cow's milk and its proteins were determined at inclusion and 6 and 12 months after finishing the desensitization protocol.

Results: Thirty-three of 36 patients were successfully desensitized (200 mL): 100% of group 1 and 88% of groups 2 and 3. Desensitization was achieved in a median of 3 months (range, 1–12 months); 90% of the patients in group 1, 50% of the patients in group 2, and 30% of the patients in group 3 achieved tolerance in less than 3 months ($P = .04$). In the control group only 1 child tolerated milk in oral food challenge after 1 year. During the induction phase, there were 53 adverse events in 27 patients (75%). Patients of groups 2 and 3 had more severe adverse events compared with group 1. During the maintenance phase, 20 of 33 patients (60%) had an adverse event.

Conclusion: Oral desensitization is efficacious. Tolerance is achieved earlier when sIgE is lower. Severe adverse events are frequent, especially in patients with higher sIgE levels.

Trial Registration: clinicaltrials.gov Identifier: NCT01641731

© 2013 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc. All rights reserved.

Introduction

Cow's milk allergy (CMA) tends to resolve by 5 years of age in up to 80% of patients.^{1–3} Reaching the age of 4 to 5 years without having achieved tolerance is a poor prognosis factor in its evolution.⁴ In recent years, some studies^{5–12} have dealt with oral desensitization, also referred as specific oral tolerance induction (SOTI). These procedures have led to restored tolerance to complete or partial amounts of the food, thus preventing unintentional reactions on ingestion of minimal amounts of the offending food.¹³ The protocols used are not risk free because the patient is subjected to undesirable reactions. This is why, before starting the protocol, it is important to thoroughly consider which patients are to be included.

The level of serum specific IgE (sIgE) is a relevant determinant in the result of oral food challenge.^{14–17} For this study, we planned to

classify patients by their serum levels of sIgE to clarify whether this parameter influences the outcome of oral desensitization to cow's milk. The aim of the study is to evaluate the efficacy of oral desensitization according to the level of sIgE and to evaluate adverse events in the induction and follow-up phases of oral desensitization.

Patients and Methods

Patients

A total of 55 children with CMA (36 boys [63%]; median age, 7 years; range, 4–14 years) were included in the study. They were diagnosed as having CMA during the first year of life and have attended periodic follow-up visits to our allergy clinic at Hospital La Paz (Madrid, Spain). Clinical data on personal history of asthma, allergy to other foods, and positive reactions on cow's milk ingestion along with their evolution from initial diagnosis were recorded.

Before inclusion in the oral desensitization protocol, determination of serum sIgE to cow's milk, α -lactalbumin, β -lactoglobulin,

Reprints: María Pedrosa, MD, Department of Allergy, Hospital La Paz, Paseo de la Castellana 261, 28046 Madrid, Spain; E-mail: maria.pedrosa@idipaz.es.

Disclosures: Authors have nothing to disclose.

and casein (ImmunoCAP, Phadia, Uppsala, Sweden) was performed, and current clinical status was confirmed by oral food challenge (OFC) with cow's milk. An open OFC with cow's milk (3 g of proteins per 100 mL) was performed starting at a dose of 0.005 mL. Doses were doubled until objective clinical reactivity was achieved.

Thirty-six children with CMA (24 boys [67%]; age, ≥ 4 years; median age, 7 years; range, 4–13 years) who agreed to participate in the oral desensitization protocol were included as the SOTI group. Determination of serum sIgE to cow's milk and its proteins was performed at the 6- and 12-month follow-up visits.

To evaluate the influence of the level of sensitization in the result of oral desensitization protocol, patients were classified into 3 groups according to the level of sIgE for cow's milk and/or its proteins: group 1, 0.35 to 3.5 kU/L; group 2, greater than 3.5 to 17 kU/L; and group 3, greater than 17 to 50 kU/L. The highest sIgE level against any of the cow's milk or its proteins determined the group of inclusion.

The control group was composed of 19 children who refused to undergo oral desensitization after the OFC. These children (12 boys; median age, 8.2 years; age range, 4–14 years), with similar levels of sIgE, were included to evaluate the natural evolution to tolerance of CMA. Six patients with sIgE levels of 0.35 to 3.5 kU/L, 6 patients with sIgE levels greater than 3.5–17 kU/L, and 7 patients with sIgE levels greater than 17 to 50 kU/L were included. They were followed for one year, after which clinical reactivity with OFC was again confirmed.

Parents or legal representatives gave written informed consent, which was approved by the local ethics committee. Protocol was registered at clinicaltrials.gov (NCT01641731).

Induction Phase

The initial dose for oral desensitization was the previous dose that elicited symptoms in the OFC. Until a dose of 1 mL was achieved, doses were increased at the hospital setting in a daily basis. From there on, doses were increased weekly at the hospital, and patients maintained this dose twice daily at home (Table 1). Achieving an intake of 200 mL of milk (6 g of proteins) twice a day, which is the usual amount for patients of that age, was considered successful desensitization.

Reactions occurring during the induction phase at the hospital were treated according to the severity of symptoms. If patients presented with mild nonobjective symptoms, the same dose was repeated. If the reaction was objective and limited to local symptoms, the previous dose was given after the resolution of symptoms. If the reaction was generalized, involving 2 organ systems, the protocol was continued with a dose that was 2 doses previous to the one that elicited symptoms. If the reaction involved 3 organ systems, the next dose administered was reduced 3 steps in the dosage protocol. Written instructions were given to parents regarding how to treat possible adverse reactions at home.

After the induction phase, patients continued to consume 200 mL milk twice daily and a free diet was allowed. In the maintenance phase, follow-up visits were scheduled at 1 month, 6 months, and

1 year after finishing the induction phase. Adverse events on cow's milk ingestion were recorded.

Statistical Analyses

The patients' characteristics and the percentage of patients who reached tolerance (200 mL) after the induction phase were evaluated and compared with the percentage of patients who reached tolerance following their natural evolution in the control group. Comparisons between qualitative variables were performed using the χ^2 test. The evolution of serum sIgE levels at the time of inclusion, at 6 months, and at 1 year after finishing the induction phase was analyzed, and comparisons were performed using the Wilcoxon test. The Mann-Whitney *U* test was used to compare differences in serum sIgE values between control and treatment groups. The statistical analysis was performed with SPSS statistical software for Windows, version 15.0 (SPSS Inc, Chicago, Illinois).

Results

Patient characteristics are listed in Table 2.

Oral Food Challenge

In the patient group, the median dose that elicited symptoms in the OFC was 27.5 mL (range, 0.4–150 mL). Sixteen patients experienced symptoms in only one organ system (3 of whom presented with bronchospasm), 18 patients in 2 organ systems, and 2 patients in 3 organ systems. Table 2 gives the results in the 3 groups.

In the control group the median dose that elicited symptoms in the OFC was 2 mL (range, 0.05–50 mL). Ten patients presented symptoms in 1 organ system, whereas 9 experienced symptoms in 2 organ systems. None of them presented with bronchospasm.

Induction Phase

Thirty-three of 36 patients (92%) successfully finished the induction phase: 10 patients in group 1 (100%), 15 in group 2 (88%), and 8 in group 3 (88%). Three patients did not reach tolerance. One patient in group 3 dropped out because of psychological stress, and 2 patients in group 2 dropped out because of repeated digestive symptoms. In the control group only 1 patient of 19 tolerated cow's milk in an OFC performed in the 1-year follow-up visit (sIgE for cow's milk at inclusion 1.52 kU/L).

The median initial dose for the induction of tolerance was 13.5 mL (range, 0.05–150 mL) in the entire group. The median initial dose of induction was 40 mL (range, 2–100 mL) in group 1, 25 mL (range, 0.05–100 mL) in group 2, and 5 mL (range, 0.2–150 mL) in group 3.

The median time of induction was 3 months (range, 1–12 months). In group 1, 9 of 10 (90%) completed induction in less than 3 months, opposed to 7 of 15 (50%) in group 2 and 3 of 8 (30%) in group 3 ($P = .04$).

During the induction phase, 27 of 36 (75%) experienced an adverse event with 1 or more doses. Thus, 53 adverse events were recorded in 27 patients (Table 3). In the group of patients with lower sIgE levels, fewer adverse events were recorded: 6 of 10 (60%) as opposed to 13 of 17 (76%) in group 2 and 8 of 9 (89%) in group 3.

When assessing the severity of symptoms, we observed that patients with higher sIgE levels had more severe symptoms. One patient in group 2 developed bronchospasm; associated respiratory symptoms occurred in 3 patients in group 2 and in 2 patients in group 3. In all cases the eliciting dose was higher than 10 mL (range, 15–50 mL).

Reactions took place in a hospital setting with increasing doses or at home with a dose previously tolerated at the hospital. Seventeen reactions were treated with oral antihistamines, 2 reactions were treated with oral antihistamines and oral corticosteroids,

Table 1
Dosing schedule in the induction phase of the desensitization protocol

Group 1		Groups 2-3	
Frequency of increases	Amount increased	Frequency of increases	Amount increased
Weekly	2 mL until 10 mL 10 mL until 50 mL 20 mL until 100 mL 30 mL until 200 mL	Daily Weekly	Doubling dose until 1 mL 2 mL until 20 mL 5 mL until 50 mL 10 mL until 100 mL 20 mL until 200 mL

Table 2
Characteristics of patients and controls

Characteristic	No. (%) ^a					P value ^b
	Controls (n = 19)	Patients (n = 36)	Group 1 (n = 10)	Group 2 (n = 17)	Group 3 (n = 9)	
Male	12 (63)	24 (67)	5 (50)	11 (64)	8 (80)	.51
Age at inclusion, mean (range), y	8 (4–14)	7 (4–13)	6.5 (5–11)	7 (4–13)	4.5 (4–10)	.42
Asthma	10 (55)	13 (36)	3 (30)	6 (35)	4 (45)	.19
Food allergies	11 (57)	19 (52)	5 (50)	7 (41)	7 (77)	.42
Atopic dermatitis	6 (31)	8 (22)	0	7 (41)	1 (11)	.29
Unintentional allergic reaction	12 (62)	31 (88)	9 (90)	14 (82)	8 (88)	.55
Total IgE, median (range), kU/L	302 (18–2456)	201 (5.4–1401)	148 (24–674)	192 (5.4–1401)	261 (57–1072)	.51
Serum sIgE, median (range), kU/L						
Cow's milk	10.8 (0.64–47)	4.7 (0.34–41.1)	1.8 (0.34–3.2)	4.7 (0.34–10.3)	22.5 (11.4–41.1)	.10
α -Lactalbumin	2.6 (0.34–43.2)	1.84 (0.34–19.5)	0.7 (0.34–3.3)	3.6 (3.4–7.7)	0.6 (0.34–19.5)	.26
β -Lactoglobulin	0.59 (0.34–17.1)	0.61 (0.34–7.5)	0.34 (0.34–1.3)	0.6 (0.34–7.5)	1.9 (0.34–4.1)	.46
Casein	5.9 (0.34–49)	2.1 (0.34–42.1)	0.7 (0.34–2.4)	2.3 (0.34–9)	19.7 (3–42)	.14
OFC dose, median, mL	2 (0.05–150)	27.5 (0.4–150)	62.5 (5–150)	50 (2–150)	7 (0.4–150)	<.001
Symptoms in OFC						
1 organ system	10 (53)	16 (44)	4 (40)	4 (24)	8 (89)	.57
≥ 2 organ systems	9 (47)	20 (56)	6 (60)	13 (77)	1 (11)	

Abbreviation: OFC, oral food challenge.

^aData are presented as number (percentage) unless otherwise indicated.

^bComparisons are made between patient and control groups.

4 reactions required inhaled bronchodilators, and 1 reaction required intramuscular epinephrine. Thirteen patients continued the protocol, repeating the dose that elicited symptoms, and 22 went back to the previous dose.

Maintenance Phase

Thirty-one patients were followed up at the first month visit and 30 patients at the 6-month and the 1-year visit. Eight patients (26%) had experienced adverse events at the 1-month visit, 6 (20%) at the 6-month visit, and 6 (20%) at the 1-year follow-up visit (Table 4). Anaphylaxis occurred in 2 patients after milk intake followed by exercise. In 3 patients reactions followed the ingestion of goat and sheep cheese. These patients belonged to groups 2 and 3, and after the reaction they continued intake of cow's milk.

Nineteen patients who underwent OFC and refused to participate in the SOTI comprised the control group. After the 1-year period of follow-up, only 1 patient tolerated cow's milk. Seven (36%) experienced unintentional allergic reactions, and 1 required treatment with epinephrine.

Evolution of sIgE Levels

A decrease in levels of sIgE from the beginning to the 1-year follow-up visit was observed, although it was only statistically significant for the levels of casein-sIgE (Table 5). In the control group, no differences were seen in the levels of sIgE from the beginning to the 1-year follow-up visit.

Table 3
Adverse events during the induction phase of the desensitization protocol

Event	Group 1 (n = 10)	Group 2 (n = 17)	Group 3 (n = 9)
No. (%) of patients	6 (60)	13 (76)	8 (89)
No. of adverse events	8	26	19
Cutaneous	6	13	8
Digestive	1	6	7
Respiratory	1	4	2
Rhinoconjunctivitis	1	3	2
Bronchospasm	0	1	0
Associated symptoms	0	3	2
Cutaneous and digestive	0	2	1
Cutaneous and bronchospasm	0	1	0
Digestive and bronchospasm	0	0	1

Discussion

Several studies have been published addressing oral tolerance induction to cow's milk.^{5–14} Their main objective was to develop methods that let patients achieve tolerance to amounts of cow's milk appropriate for their age, without developing allergic symptoms. In these studies, the methods and protocols vary, and thus, the results are not comparable. The main variations include patient characteristics (age, severity of the reactions, and level of sensitization) and the methods and protocols used in SOTI.

CMA is a dynamic process that begins in the first year of age, coinciding with the introduction of these proteins in the diet. The natural evolution of CMA is to achieve tolerance as the years go by. Eighty percent^{1–3} of patients become tolerant by 5 years of age. Nevertheless, there are other patients who have a poor evolution, whose sIgE levels continue to increase, and who continue having unexpected reactions, in some cases presenting with anaphylaxis. For this reason, when evaluating results, age is an important variable to be taken into account. In the study by Martorell et al,⁸ performed on children 2 years old, evolution of CMA after SOTI was good (90% achieved tolerance). However, in this pediatric population, it is likely that some children developed tolerance spontaneously. In addition, performing SOTI in children of this age may have prevented a poorer evolution. As children grow up, there is an increase in sIgE levels, and sensitization to other foods and inhalant allergens may play a role. Thus, these patients should be monitored in their evolution. Most studies related to SOTI include children 4 years or older.

Table 4
Adverse events during the maintenance phase

Event	1-Month visit	6-Month visit	1-Year visit
No. (%) of adverse events	8/31 (26)	6/30 (20)	6/30 (20)
Symptoms, No.			
Oropharynx pruritus	3	2	4
U/AE	1	1	0
Abdominal pain	2	1	1
Anaphylaxis	2	2	1
Offending product			
Milk	5	5	4
CM cheese	1	0	0
SM or GM cheese	2	1	2

Abbreviations: CM, cow's milk; GM, goat's milk; SM, sheep's milk; U/AE, urticaria and/or angioedema.

Table 5

Evolution of serum specific IgE in the study groups

Variable	Specific IgE, median (range), kU/L							
	Desensitization group				Control group			
	T0	T6	T12	P value (T0-T6)	P value (T0-T12)	T0	T12	P value (T0 SOTI-control) P value (T12 SOTI-control)
Total IgE	201 (5.4-1401)	266 (21-2185)	375 (18-1389)	.005	.004	302 (18-2456)	478.5 (43-1715)	.51
slgE cow's milk	4.6 (0.34-41.1)	3.6 (0.34-37.5)	3.0 (0.78-41.2)	.94	.003	10.8 (0.64-47)	6.3 (0.34-59)	.147
slgE α -lactalbumin	1.8 (0.34-19.5)	2.2 (0.34-12.5)	1.34 (0.34-23.7)	.42	.09	2.6 (0.34-43.2)	1.89 (0.34-56.0)	.26
slgE β -lactoglobulin	0.48 (0.34-7.57)	0.6 (0.34-10.5)	0.57 (0.34-13.3)	.21	.91	0.59 (0.34-17.1)	1.62 (0.34-90.3)	.46
slgE casein	2.4 (0.34-42.1)	1.4 (0.34-12.4)	1.17 (0.34-9.3)	.001	<.001	5.9 (0.34-49)	4.5 (0.34-52.9)	.19

Abbreviations: slgE, specific IgE; SOTI, specific oral tolerance induction; T0, inclusion visit; T6, 6-month visit; T12, 1-year visit.

Another important variable when evaluating these studies is the severity of symptoms. In the study by Longo et al,⁶ only children with a severe history of allergy to cow's milk were included. These patients had higher levels of sensitization. The results of SOTI were poorer than previously reported⁸ because complete tolerance was achieved in just 36% of the children, and partial tolerance was achieved in 54%.

In our study, we analyzed and controlled the results for the level of sensitization, and thus we classified patients into 3 groups. In children with a higher level of slgE (group 3) asthma was more prevalent, as was allergy to other foods. The initial dose of oral desensitization protocol was lower in this group of patients because they reacted to a lower dose in the OFC. Two different dosing schedules (Table 1), according to slgE levels, were used in the induction phase to shorten the desensitization protocol.

In the induction phase, results were better in patients than in the control group. In the desensitization group, tolerance was achieved in 92% of patients, whereas only 1 patient of 19 (5%) in the control group tolerated CM after 1 year of follow-up. The control group reacted to a lower dose in the OFC than did patients, although the symptoms elicited were not more severe, and none of the individuals in the control group required epinephrine to treat the reaction. Although slgE was slightly higher in the control group, the differences were not statistically significant. The fact that the eliciting dose in the initial OFC was lower in the control group may have biased the results, but the difference in the proportion of individuals who developed tolerance in each group is so high that the possible bias would not invalidate the results.

An important variable to be considered at the time of initiation of desensitization protocols is the slgE level to cow's milk, which may determine the outcome of the desensitization protocol. According to Staden et al,⁵ children with low or moderate levels of slgE will have a better evolution.

Zapatero et al,⁹ using a protocol that lasted a mean of 14 weeks, obtained tolerance in 16 of 18 patients (88%) older than 4 years. They had a median slgE to cow's milk of 4.5 kU/L, similar to that observed in our patients.

In addition to the percentage of patients who achieve tolerance, in the evaluation of desensitization protocols the occurrence of adverse events is an important factor. In the group with lower levels of slgE against cow's milk, a lower rate of adverse events was observed, although no statistical significance was observed. Adverse reactions in this group were also less severe because none of them involved 2 or more organs. In the entire group only 3 patients refused to continue with the protocol because of the symptoms they had experienced. None of these patients belonged to group 1. Most of these adverse reactions took place in the hospital setting, when the higher dose was given. Adverse events that took place at home only required treatment with oral antihistamines.

Adverse events are not predictable. Depending on the level of sensitization, the induction protocols need to be adapted at home

in some cases or in hospital settings in others, although this option is costly for patients who may therefore need more hospital visits.

The higher the slgE level, the more severe the adverse events during the induction phase. In our patients, the most severe adverse events developed with doses between 15 and 50 mL. For these reasons patients must be strictly supervised until the protocol is completed.

Follow-up

Once tolerance was achieved, in the maintenance phase we observed some adverse events during the first few months.

There are a few cases of anaphylaxis upon ingestion of cow's milk followed by exercise.^{18,19} In our study, 2 patients in group 1 had anaphylaxis with exercise after the ingestion of milk. One of these reactions took place 1 month after achieving tolerance and the other after 3 months of follow-up. In this last reaction, the pollen season, which has been described as a possible triggering factor, may have been the eliciting factor.⁵ This patient went back on a cow's milk restricted diet because of a fear of reactions.

Although patients achieve tolerance to cow's milk, they must be strictly monitored and should be warned of this possibility. Exercise after the ingestion of cow's milk should be avoided until the sensitization subsides. Cheese is a common food in our diet. There are reports of allergic children who tolerated cow's milk after SOTI who developed symptoms after ingestion of goat's milk (GM) and sheep's milk (SM) cheese.²⁰ In our study we observed that most children refused to taste GM or SM cheese, and the few patients who did try them developed symptoms. Allergenicity of GM or SM cheese is mainly due to casein. There is a high degree of cross-reactivity between caseins of different mammals because of the high gene sequence homology. For this reason, these patients will have to avoid these products until sensitization is outgrown or until tolerance to these cheeses is assessed in a hospital setting.

Evolution of slgE

In the follow-up of slgE levels, a decrease in slgE against all cow's milk proteins was observed, but it was only significant for casein. In studies of clinical allergic reactivity, low casein slgE levels have been reported to be a marker of progress toward tolerance, so this decrease could be considered a marker of good evolution in our series. With this protocol, we could induce tolerance that otherwise would not have been achieved. In the control group, after the 1-year follow-up we did not observe a similar decrease in slgE levels, and patients developed symptoms on unintentional ingestion. Monitoring slgE levels until they become negative will indicate a good evolution.

Mechanisms underlying the induction of tolerance are not well known. Some authors believe that a desensitization status is achieved, as has been reported for subcutaneous immunotherapy with inhalant allergens, and thus this status may be permanent. However, it has also been proposed that oral tolerance is due to tachyphylaxis

and that the tolerance achieved would only be maintained by continuous exposure to the food. In the study by Staden et al,⁵ an OFC was performed after 2 months of a cow's milk-free diet; permanent tolerance was confirmed in 36% of the patients, 12% tolerated the maintenance dose but developed symptoms after the avoiding period, and 16% were found to be partially tolerant. Skripak et al⁷ found that all their patients experienced an increase in the minimal dose that elicited symptoms after SOTI.

Results in terms of tolerance are better in patients who followed a desensitization protocol than in those left to their natural evolution, so we believe that, although not risk free, this treatment is efficacious. Nevertheless, it is necessary to use similar or standardized protocols to have comparable results that lead to generalizable conclusions.

To summarize, the level of circulating sIgE is important in the induction of specific oral tolerance because the results may vary. Once tolerance is achieved, more severe adverse reactions were found to appear after exercise and on ingestion of GM and SM cheese. More studies are needed before oral desensitization can be recommended as routine clinical practice. Long-term follow-up studies are needed to confirm persistent tolerance.

References

- [1] Host A. Cow's milk protein allergy and intolerance in infancy. Some clinical, epidemiological and immunological aspects. *Pediatr Allergy Immunol*. 1994;5: 1–36.
- [2] Bishop JM, Hill DJ, Hosking CS. Natural history of cow's milk allergy: clinical outcome. *J Pediatr*. 1990;116:862–867.
- [3] Sampson HA. Food allergy, part I: immunopathogenesis and clinical disorders. *J Allergy Clin Immunol*. 1999;103:717–728.
- [4] García-Ara MC, Boyano-Martínez T, Martín-Muñoz F, Martín E, Díaz Pena JM, Ojeda JA. Actitud terapéutica y pronóstico en la alergia a alimentos. *Allergol Immunopathol*. 1996;24(suppl 1):31–35.
- [5] Staden U, Rolinck-Werninghaus C, Brewe F, Wahn U, Niggemann B, Beyer K. Specific oral tolerance induction in food allergy in children: efficacy and clinical patterns of reaction. *Allergy*. 2007;62:1261–1269.
- [6] Longo G, Barbi E, Berti I, et al. Specific oral tolerance induction in children with very severe cow's milk-induced reactions. *J Allergy Clin Immunol*. 2008; 121:343–347.
- [7] Skripak JM, Nash SD, Rowley H, et al. A randomized double-blind, placebo controlled study of milk oral immunotherapy for cow's milk allergy. *J Allergy Clin Immunol*. 2008;122:1154–1160.
- [8] Martorell A, De la Hoz B, Ibáñez MD, et al. Oral desensitization as a useful treatment in 2-year-old children with cow's milk allergy. *Clin Exp Allergy*. 2011;41:1297–1304.
- [9] Zapatero L, Alonso E, Fuentes V, Martínez MI. Oral desensitization in children with cow's milk allergy. *J Investig Allergol Clin Immunol*. 2008;18(5):389–393.
- [10] Fisher HR, Du Toit G, Lack G. Specific oral tolerance induction in food allergy children: is oral desensitization more effective than allergen avoidance? *Arch Dis Child*. 2011;96:259–264.
- [11] Meglio P, Bartone R, Plantamura M, Arabito E, Giampietro PG. A protocol for oral desensitization in children with IgE mediated cow's milk allergy. *Allergy*. 2004;59:980–987.
- [12] Rolinck-Werninghaus C, Staden U, Mehl A, et al. Specific oral tolerance induction with food in children: transient or persistent effect on food allergy? *Allergy*. 2005;60:1320–1322.
- [13] Patriarca G, Nucera E, Roncallo C, et al. Oral desensitizing treatment in food allergy: clinical and immunological results. *Aliment Pharmacol Ther*. 2003;17: 459–465.
- [14] Niggemann B, Staden U, Rolinck-Werninghaus C, Beyer K. Specific oral tolerance induction in food allergy. *Allergy*. 2006;61:808–811.
- [15] Boyano-Martínez MT, García-Ara MC, Pedrosa M, Díaz-Pena JM, Quirce S. Accidental allergic reactions in children allergic to cow's milk proteins. *J Allergy Clin Immunol*. 2009;123:883–888.
- [16] Sampson HA, Ho DG. Relation between food-specific IgE concentrations and the risk of positive food challenges in children and adolescents. *J Allergy Clin Immunol*. 1997;100:444–451.
- [17] García-Ara MC, Boyano-Martínez T, Díaz Pena JM, Martín-Muñoz F, Reche Frutos M, Martín E. Specific IgE levels in the diagnosis of immediate hypersensitivity to cow's milk proteins in the infant. *J Allergy Clin Immunol*. 2001; 107:185–190.
- [18] García-Ara MC, Valls-Sánchez A, Boyano-Martínez MT, Díaz-Pena JM. Cow's milk-dependent exercise-induced anaphylaxis: case report of a patient with previous allergy to cow's milk. *J Allergy Clin Immunol*. 2003;111:647–648.
- [19] Caminiti G, Passalacqua G, Vita D, Ruggeri P, Barberio G, Pajno GB. Food-exercise-induced anaphylaxis in a boy successfully desensitized to cow milk. *Allergy*. 2007;62:335–336.
- [20] Alonso-Lebrero E, Fuentes V, Zapatero L, Perez-Bustamante S, Pineda F, Martínez-Molero MI. Goat's milk allergies in children following specific oral tolerance induction to cow's milk. *Allergol Immunopathol*. 2008;36:180–181.