

Specific oral desensitization in children with IgE-mediated cow's milk allergy. Evolution in one year

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Abstract Cow's milk allergy is the most frequent childhood food allergy. Children older than 5 who have not become tolerant have less probabilities of natural tolerance. Specific oral desensitization methods are being investigated in reference centres. The aims of our study were to assess the efficacy of our guideline of specific oral desensitization to cow's milk in children and to know its suitability for anaphylactic children. Both clinical and specific IgE outcomes were evaluated. Eighty-seven children aged 5 to 16 years with a history of cow's milk allergy were included. Prior to desensitization, skin prick test, specific IgE to cow's milk proteins and a double-blind placebo control food challenge were performed in all. Of the 87 patients, 21 had a negative challenge; they were considered tolerant, and they were told to follow a free diet. Of the positive, 44 were anaphylactic and 22 non-anaphylactic. All of them were included. In non-anaphylactic patients, 6 achieved partial and 16 maximum desensitization after 23.1 weeks. In the anaphylactic group, 7 achieved partial and 35 maximum desensitization after 26.4 weeks. Cow's milk-specific IgE levels and casein-specific IgE levels were significantly lower in the tolerant patients at baseline. One year after desensitization, the medium specific cow's milk levels and casein IgE levels had dropped significantly. **Conclusions:** Our guideline for specific oral desensitization to cow's milk is efficacious even in patients with anaphylactic reactions to cow's milk and represents a significant life

change. Immunological changes in 1 year show a drop in cow's milk protein-specific IgE.

Keywords Cow's milk allergy · Cow's milk-specific IgE · Anaphylaxis · Oral immunotherapy · Specific oral desensitization · Specific oral tolerance induction

Introduction

Nowadays, food allergy (FA) is a new epidemic with important implications. Cow's milk allergy (CMA) is universally the most common food allergy in the first years of life [25], affecting 2 to 3 % of the general population [28]. Although the prognosis is good with a remission rate about 45–50 % at 1, 60–75 % at 2 and 85 % at 3 years of age [6], there are still some children who do not outgrow their allergy at the age of 10.

Resolution of symptoms during strict cow's milk protein (CMP) avoidance and their reappearance during the double-blind placebo control food challenge (DBPCFC) remain the gold standard for the diagnosis of CMA [26]. Food allergy is the primary cause of anaphylaxis in children, and in Europe, CMP and hen's egg proteins are the main offenders [35]. A treatment that could modify the natural history of food allergy by inducing long-term tolerance would be of great benefit to patients who fail to outgrow their allergy [32]. Oral tolerance to foods is one of the most significant challenges that the immune system faces, and its understanding is crucial [34]. An anergy state or death in reactive T cells has been demonstrated. Natural regulatory CD4⁺ T cells, inducible regulatory CD4⁺ T cells, TGF- β -secreting Th3 cells and IL-10-producing B cells are included in this process. Children with food allergies exhibit reduced numbers of circulating IL-10-producing cells and TGF- β -producing T cells within their intestinal mucosa [7, 19].

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Until very recently, a single approach was available for the treatment of food allergy: avoidance of the offending food [36]. A number of promising therapeutic modalities for food allergy are now emerging, including allergen-specific immunotherapeutic approaches which attempt to induce tolerance [27]. Although studies suggest that most patients with FA can be desensitized with oral immunotherapy, no studies have demonstrated the development of tolerance [14].

In Europe, the oral exposure to increasing doses of the food is preferably termed specific oral tolerance induction. We believe that a better term would be “specific oral desensitization (SOD)” as we still do not know when permanent tolerance will be reached. In the USA, the term preferred is oral immunotherapy. It is thought, though, that its mechanisms of action differ from those of specific immunotherapy to inhalants [2]. Immunological changes accompanying oral desensitization include decreased reactivity of mast cells and basophils, increased food-specific IgG4 antibodies and decreased food-specific IgE antibodies [14].

The offending food is administered orally, starting with very low doses, which are increased up to the usual intake. Thereafter, the food is given daily in a maintenance dosage [13]. After SOD, the threshold dose for allergic reaction is increased considerably [30]. This approach should be conducted by an experienced allergy specialist and closely monitored. At present, SOD to food is one of the most actively investigated therapeutic approaches for food allergy, although few trials have established patient reactivity before therapy, including a placebo control food challenge [14].

The aims of our study were to assess the efficacy of the Spanish Paediatric Clinical Immunology and Allergology Society (SEICAP) Guidelines for SOD to CMP in children and to know its suitability for anaphylactic children. Both clinical and specific IgE outcomes (at inclusion and 1 year after SOD) were evaluated.

Materials and methods

Study population

Eighty-seven children (53 males, 34 females) aged 5 to 16 years old (mean age, 8 years) with a known history of IgE-mediated cow's milk (CM) allergy were recruited consecutively from the Paediatric Allergy and Clinical Immunology Section at the Sant Joan de Deu Hospital in Barcelona, Spain. They were admitted to the study from October 2006 to November 2009. Forty eight (55.1 %) had a history for at least one anaphylactic reaction after exposure to CMP, requiring epinephrine. Concomitant diseases were: asthma, 43 %; allergic rhinitis, 39 %; atopic

dermatitis, 63 % and other food allergies, 83 % (the most prevalent were egg, tree nuts and shellfish).

Study design and methods

Diagnosis of CMA was based on (1) positive DBPCFC, (2) positive clinical history, (3) positive skin prick test (SPT) to CMP and (4) cow's milk-specific IgE levels for whole milk and the major cow's milk allergens (α -lactalbumin, β -lactoglobulin and casein) (CAP-Phadia, Uppsala, Sweden). Skin tests were performed on the forearm with commercial extracts (Stallergenes Iberica, S.A.). Wheals were measured by scanner using a Prick Film method (Immunotek, Madrid). A wheal of ≥ 3 mm (major diameter) was considered positive according to the EAACI position paper guidelines. Specific IgE levels to CMP greater than 0.35 kU/L were also considered positive. SPT and CMP-specific IgE levels were performed at baseline (before SOD) and repeated 1 year after in all patients.

All patients underwent a DBPCFC in the hospital before SOD. This procedure [15] started with very low amounts of diluted cow's milk cooked with mashed potatoes. The placebo consisted of the same food cooked with soy formula. The doses were administered increasingly every 60 min. The challenge procedure was stopped when clear clinical symptoms appeared or when the highest dose was reached (200 cc). Emergency medications including epinephrine, hydroxyzine, salbutamol and prednisone were available. The symptoms evaluated were itching, urticaria, angioedema, exacerbation of eczema, rhinitis or conjunctivitis, dyspnea and wheezing, vomiting, diarrhoea and hypotension. They were scored by a paediatric allergy specialist. Children were classified as anaphylactic if they have had an anaphylactic reaction requiring epinephrine during the DBPCFC [12, 24, 33] and non-anaphylactic otherwise.

Children were considered eligible for SOD only if they had symptoms during the DBPCFC. The span of time between the last spontaneous milk reaction and the DBPCFC was, at least, 1 year. Parents of all children signed an informed consent, and the study was approved by the ethics committee of Sant Joan de Deu Hospital.

Statistical analysis

Data are presented as mean values and 95 % CI. The data were statistically evaluated by analysis of variance, one way with three levels (tolerant, anaphylactic, non-anaphylactic). Subsequently, we compared all possible pairs of subgroups using the multiple comparisons Tukey's method. The comparison of specific IgE values is presented using Student's *t* test for paired data. A *p* value of less than 0.05 was considered significant for all comparisons.

SOD protocol

The SEICAP guidelines [9] to SOD to CMP were followed. No premedication was given.

Children were hospitalized for the desensitization, which involved increasing amounts of CMP. On the first day, there were given 1, 2, 4, 8 and 16 cc of whole CM diluted 1:100 with water at 1-h intervals. On the second day, 1.5, 3, 6 and 12 cc of whole CM diluted 1:10 at 1-h intervals and, finally, 2.5 cc of CM without dilution. The patients were then discharged continuing with the last dosage tolerated on a one or two daily basis (when possible) throughout the week. Subsequently, they came to the hospital once a week to increase the doses: 4, 6, 8, 10, 12, 15, 20, 25, 30, 40, 50, 75, 100, 125, 150 and 200 cc. They remained under medical supervision, for at least 2 h. The dose was never given on an empty stomach. Patients were recommended to avoid exercise for 3 h after milk intake. If there was an intercurrent illness, the milk dose was not increased, and the previous dose was repeated. Parents and patients were instructed in the recognition of adverse reactions, the assessment of their severity and their treatment with antihistamines and epinephrine with written instructions. If the patient had a moderate and/or severe symptom, he/she was told to go one step backwards in the dose intake the week after. The procedure was stopped when the patients were able to tolerate 200 mL once a day. From then on, they were kept on a schedule of at least 200 mL daily.

Results

Of the 87 patients, 21 had a negative DBPCFC; thus, they were considered tolerant to cow's milk and told to follow a free diet. Their mean age was 7.9 years. In 66 patients, the DBPCFC was positive; 44 of them were anaphylactic and 22 non-anaphylactic. All of them were included in the study. Their mean age was 8.1 years (Fig. 1).

The grade of anaphylaxis that occurred with the DBPCFC was: mild, 12 cases; moderate, 27 cases and severe, 5 cases. Guidelines in the position paper of the European Academy of Allergy and Clinical Immunology were followed to classify and treat these reactions [12].

At the inclusion, the mean specific CM IgE level was 61.15 kU/L (range, 0.40–840 kU/L), and the mean casein IgE level was 72.72 kU/L (range, 0.38–1,230 kU/L) in all groups (Fig. 2). The mean CM-specific IgE level in the tolerant patients ($n=21$) was 7.35 kU/L (95% CI 1.02–13.68), and the mean casein-specific IgE level was 5.95 kU/L (95 % CI 2–9.9).

The 44 anaphylactic patients had mean specific IgE levels, at the inclusion, as follows: CM IgE, 101.85 kU/L (95 % CI 57.32–146.38) and casein IgE, 125.62 kU/L (95 % CI 61.50–189.74). The non-tolerant, non-anaphylactic

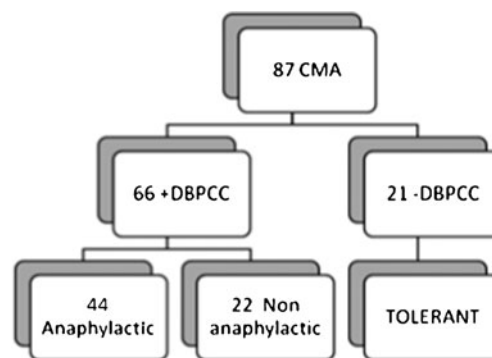


Fig. 1 Of the 87 patients enrolled for the study, 21 had a negative DBPCFC; they were considered as tolerant and were told to follow a free diet. In 66 patients, the DBPCFC was positive; 44 of them were anaphylactic and 22 non-anaphylactic

patients ($n=22$) had CM IgE levels of 31.1 kU/L (95 % CI 10.47–51.73) and casein IgE 30.6 kU/L (95 % CI 8.53–52.67). Patients with anaphylaxis during DBPCFC had significantly higher levels of CM-specific IgE ($p=0.006$) and casein-specific IgE ($p=0.01$) than the tolerant group. The difference was also statistically significant between anaphylactic patients and non-tolerant non-anaphylactic patients, with $p=0.02$ for specific CM IgE and $p=0.03$ for specific casein IgE.

One year after the first laboratory data, new blood samples were obtained. In the non-tolerant anaphylactic patients ($n=44$), the medium specific CM levels dropped from 101.85 kU/L (95 % CI 57.32–146.38) to 31.97 kU/L (95 % CI 17.78–46.16) ($p=0.006$) and casein IgE levels from 125.62 kU/L (95 % CI 61.50–189.74) to 33.2 kU/L (95 % CI 13.46–52.94) ($p=0.01$). In the non-tolerant, non-anaphylactic patients ($n=22$), the medium specific CM IgE levels dropped from 31.1 kU/L (95 % CI 10.47–51.73) to 8.3 kU/L (95 % CI 4.4–12.24) ($p=0.06$) and casein IgE levels from 30.6 kU/L (95 % CI 8.53–52.67) to 7 kU/L (95 % CI 2.25–11.75) ($p=0.07$) (Figs. 3 and 4).

CM tolerance (with ongoing exposure to CM) in enrolled patients was determined based on current guidelines [8]: maximum tolerance (150 mL CM or more in a single dose), partial tolerance (5–149 mL CM in a single dose) and non-tolerant (<5 mL).

In the 22 non-anaphylactic patients with a positive DBPCFC, 16 reached maximum tolerance and 6 only partial, and the process was completed in 23.1 weeks. In the anaphylactic group ($n=44$), 35 patients reached maximum tolerance, 7 partial, 1 only tolerates 2 cc and there has been one withdrawal. The time required to reach these doses was 26.4 weeks.

Discussion

Our study provides data on rates of desensitization in the largest group of patients published until now. Oral tolerance

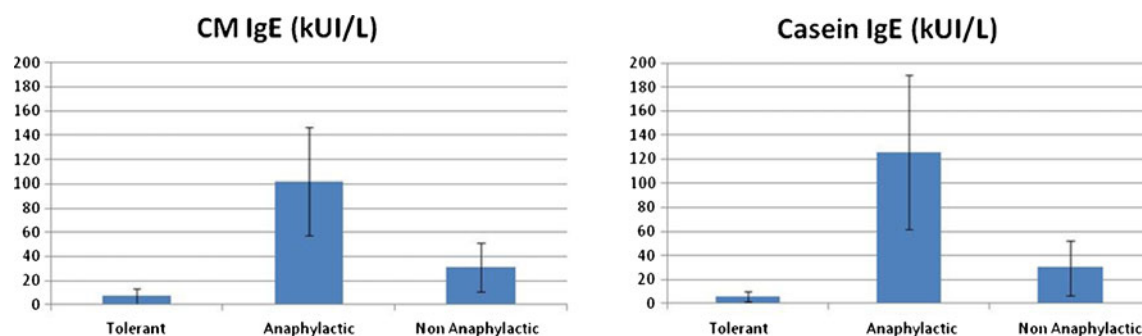


Fig. 2 Differences in baseline specific IgE levels between tolerant and non-tolerant patients in DBPCFC

is the active non-response of the immune system to an antigen administered through the oral route. The term “tolerance” is understood as a condition in which a patient has outgrown his food allergy either spontaneously or after receiving a desensitization treatment. As the number of children with persistent food allergy increases, approaches to treatment beyond avoidance strategies are needed.

The dramatic increase of exclusion diets in the last years may explain the increase in food allergy and anaphylaxis [1]. We have little evidence-based guidance about when to introduce allergens in the diet and whether to introduce these foods in large or small quantities, regularly or irregularly. Animal studies suggest that the high-dose feeding of an antigen results in non-responsiveness due to anergy or deletion of antigen-specific T lymphocytes, whereas continuous low-dose ingestion may induce protective suppressive responses from regulatory T cells [3]. On the other hand, intermittent feedings or non-oral exposures can induce IgE sensitization and also symptoms after food ingestion [31].

As a subset of children with food allergies develops tolerance spontaneously, the studies must address diagnostic tests that would distinguish among those with transient and persistent food allergies [16]. Excessive use of skin tests and specific IgE assays, without proper criteria, causes inadequate management. Despite the risk to which the child is exposed, and because of the absence of specific tests, oral challenge is still considered the gold standard to diagnose

CMA [4]. This study is one of the few which establishes patient's reactivity before therapy, including a placebo control food challenge. It adds information on this item, and we conclude that it should be mandatory to perform a DBPCFC in children 5 years old and older with cow's milk allergy as, even though, the mean specific IgE levels are lower in tolerant patients, there are still those in whom this did not predict spontaneous tolerance. In 1997, Sampson and coworkers [22, 23] published the first of two studies that proposed 90 and 95 % PPVs for milk relating to specific CM IgE values. These proposed thresholds have been of great value in the food challenge decision-making process. Although in our study the level of specific IgE has been a good indicator of spontaneous tolerance, a few children who passed the DBPCFC had very high sIgE levels making these values not reliable in these specific cases. In other studies [5], a significant relationship was found between the challenge dose and CM-specific IgE. Children who had reactions with the smallest dose in the challenge test had the higher CM-specific IgE levels.

A 6-year-old (or older) child who is still suffering from an IgE-mediated allergy to CM has a low probability of recovering spontaneously in a short time [10], and this is also why we propose to perform a DBPCFC in all children above 5 before starting the SOD. We have found that 21 of the 87 patients (24.1 %) included were tolerant when submitted to the DBPCFC.

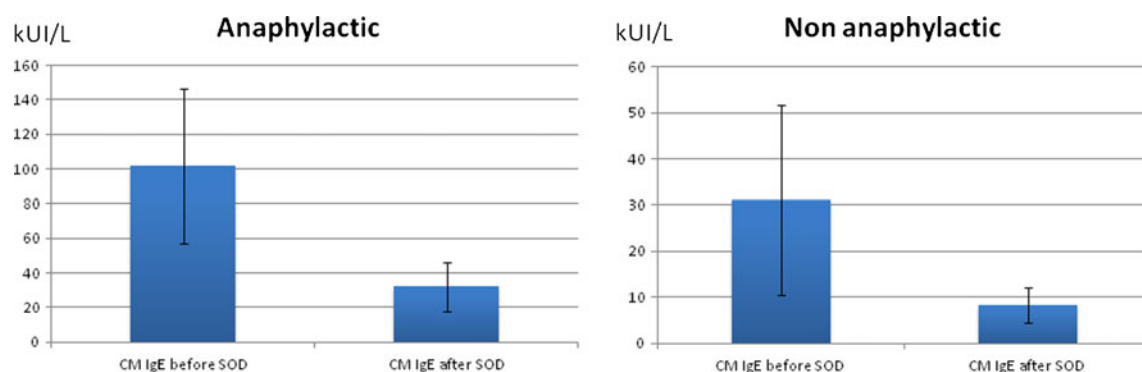


Fig. 3 Marked decrease in CM IgE values 1 year after SOD start in anaphylactic and non-anaphylactic patients

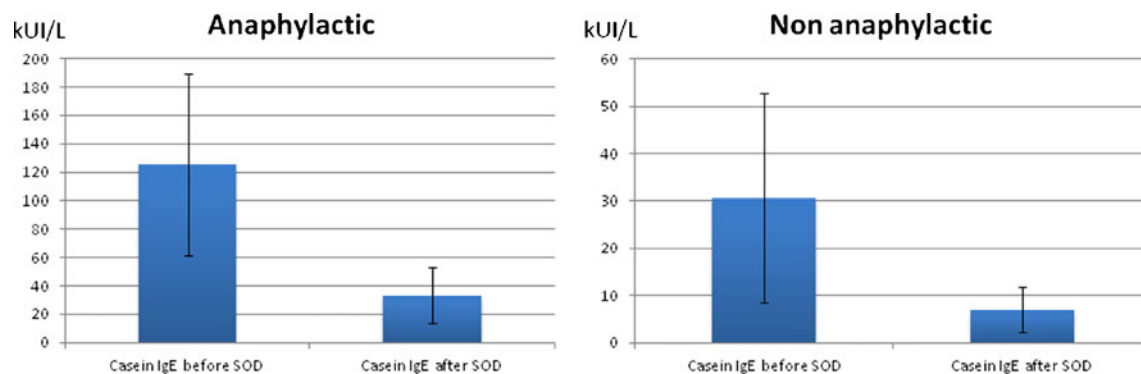


Fig. 4 Marked decrease in casein IgE values 1 year after SOD start in anaphylactic and non-anaphylactic patients

Children with low to moderate specific IgE levels would be expected to respond better to SOD compared to patients with high specific IgE levels. Nevertheless, these high risk patients would probably be those with the greatest benefit since they are most likely to have persistent food allergy and their reactions can be life threatening [13]. Other authors found difficulties in CM-SOD of patients with high sIgE [8, 10, 18, 27, 30] and asthma/rhinoconjunctivitis [30]. A further research on a larger sample of CM-desensitized children focused on safety and clinical and immunological predictors of adverse events during CM-SOD is being developed by our group. One year after the oral desensitizing process, we observed a significant decrease in specific CM IgE and casein-specific IgE, reflecting a change in the immunological background.

Preliminary studies on SOD have shown promising results with efficacy rates between 75 and 86 %. Patriarca showed rates of success in CM desensitization of 79.2 % [18]. Patients received sodium cromoglicate. The control group DBPCFC remained positive in all cases after the placebo treatment. In the study by Meglio [10], the success rate was 71.4 %. Patients received cetirizine, and a control group was not included. In the study by Longo [8], in children with severe CM-induced reactions, 36 % became completely tolerant and 54 % could ingest limited amounts of milk (5–150 mL). These children received antihistamines during the desensitization process. There was a control group in which 100 % had a positive DBPCFC after 1 year. Although 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 [8]. In the study by Pajno, 77 % of the children in the active group reached the 200-mL dose without adverse events. The dose was administered weekly. None of the children in the control group achieved even partial tolerance. Their age was 4–10 years, and they did not receive premedication [17]. On the other hand, a study by Morisset [11] showed a spontaneous recovery of 60 % in the control group. Children in the active

group reached complete tolerance in 88.9 % of cases. In this study, only children tolerating at least 60 mL of milk on a baseline food challenge were included, and the ages were from 13 months to 6 years. These two items make the study non-comparable with the previous ones or with our study in which ages are older than 5 and the DBPCFC at baseline was positive with little amounts of milk in all of them. The same happened in another trial by Staden [30] with a mean age of 2.5 years. The effectiveness of SOD was 64 %, and in the control group, 35 % were tolerant after 18–24 months. Zapatero et al. [37] showed a rate of complete tolerance after SOD of 89 %. Patients were treated in an outclinic, and there was no control group.

In a randomized, placebo-controlled clinical trial by Skripak [29] (ages 6–21; mean age, 9 years), none of the patients in the control group were able to tolerate milk, while in the active group, all of them tolerated a median of 154 mL (5,140 g). Another study by Caminiti [2] (ages 5–10 years) also showed no remission rate in the control group treated with placebo (soy formula). The success in the active group was 80 %. No premedication was given, and the inclusion of patients was based on the diagnosis of severe CMA.

Finally, in the last study published by Martorell et al. [9], 90 % of the children included achieved complete tolerance after 1 year of SOD while in the control group, only 23 % achieved it. However, once again, the children included were younger than ours (24–36 months) with more probabilities of spontaneous recovery.

Although we know that the weak point in our design was the absence of a control group, in the previous studies which are comparable to ours (by means of children's age—older than 5—and severity of CMA), the results of non-tolerance in all the control groups make the absence justified.

The results of the SOD studies, although encouraging, still have to answer several major questions regarding safety, the potential to induce long-term tolerance and whether these treatments will be safe and effective in those with the most severe forms of food allergy [36].

Our study shows that the schedule used to induce desensitization to cow's milk proteins is efficacious. Most of the patients (96 %) achieved enough tolerance levels to follow a diet without restrictions in milk-containing products: 77.2 % reached maximum tolerance and 19.6 % can have limited amounts of milk (partial tolerance, 5–149 cc of milk). In our patients with severe CM-induced reactions (anaphylactic), the mean time required to reach tolerance was 26.4 weeks, whereas the children who had mild reactions achieved tolerance in a mean period of 23.1 weeks. The minimum duration for the induction phase was 1 month and the maximum 14 months. For the subgroup of anaphylactic patients, both in the study by Longo et al. [8] and in ours, the odds of ever outgrowing the allergy would be small and the risk of future severe reactions high. Under these circumstances, and the SOD treatment being safe under the conditions we exposed (hospitalization, with close supervision and monitoring), this approach would be justified. Longo et al. [8] and we believe that the more severe the food allergy is and the more common the implicated food, the better the cost/benefit ratio is for SOD approach, including anaphylactic patients. Another manuscript is in progress by our group, in which we describe the adverse reactions that happened during the study. Although these were frequent (59 %) and sometimes severe, they could be easily controlled with the usual medication.

SOD can induce transient tolerance in food allergy but does not necessarily lead to its permanent abrogation. Regular allergen intake seems necessary to maintain the established tolerance [20]. SOD does not alter the natural outcome of food allergy but increases the threshold dose necessary to elicit allergic symptoms. In our study, all children included but one are able to follow a diet without restrictions in milk-containing products, and the ones with a past history of severe reactions to CM can, at least, improve their quality of life.

In conclusion, this study adds information on food immunotherapy and confirms that SOD is, nowadays, the best alternative to exclusion diet in CMA. The majority of patients (96 %) achieved desensitization to CM proteins and even the ones considered as anaphylactic had a good response to this therapeutic option. We do not know for how long the regular intake of milk must be followed, and we think that studies must be conducted in this way. We believe the experience in reference centres should always be communicated in order to add new data before the procedure can be used in the routine clinical practice. Although there is much interest in oral desensitization, a lot remains to be done. The meta-analysis made by Rona [21] about food allergy prevalence highlights the need for a collaborative study using similar methods. The ultimate goal of food allergy therapy is permanent oral tolerance, which is established when the food can be ingested without allergic

symptoms despite prolonged periods of avoidance. Could oral immunotherapy or specific oral tolerance induction with baked foods be the answer?

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Conflict of interest The authors declare that they have no conflict of interest.

References

1. Barbi E, Gerarduzzi T, Longo G, Ventura A (2004) Fatal allergy as a possible consequence of long-term elimination diet. *Allergy* 59:668–669
2. Caminiti L, Passalacqua G, Barberi S, Vita D, Barberio G, De Luca R, Battista G (2009) A new protocol for specific oral tolerance induction in children with IgE-mediated cow's milk allergy. *Allergy Asthma Proc* 30:1–6
3. Chehade M, Mayer L (2005) Oral tolerance and its relation to food hypersensitivities. *J Allergy Clin Immunol* 115:3–12
4. Fernandes AJ, Cavalcanti ES, Farias ME, Nogueira P, De Oliveira SM, Pontes GA (2011) Allergy to cow's milk proteins: what contribution does hypersensitivity in skin tests have to this diagnosis? *Pediatr Allergy Immunol* 22:e133–e138
5. Garcia-Ara MC, Boyano MT, Díaz-Pena JM, Quirce S (2008) Eliciting doses of positive challenge test in cow's milk allergy are related to cow's milk specific IgE levels. *Allergol Immunopathol* 36(6):315–319
6. Host A, Halken S, Jacobsen HP, Christensen AE, Herskinda M, Plesner K (2002) Clinical course of cow's milk protein allergy, intolerance and atopic diseases in childhood. *Pediatr Allergy Immunol* 13(Suppl 15):23–28
7. Kamdar T, Bryce PJ (2010) Immunotherapy in food allergy. *Immunotherapy* 2(3):329–338. doi:10.2217/imt.10.15
8. Longo G, Barbi E, Berti I, Meneghetti R, Pittalis A, Ronfani L, Ventura A (2008) Specific oral tolerance induction in children with very severe cow's milk-induced reactions. *J Allergy Clin Immunol* 121:343–347
9. Martorell A, De La Hoz B, Ibañez MD, Bone J, Terrados MS, Michavila A, Plaza AM, Alonso E, Garde J, Nevot S, Echevarria L, Santana C, Cerda JC, Escudero C, Guallar I, Piquer M, Zatatato L, Ferre L, Bracamonte T, Murie L A, Martinez MI, Felix R (2011) Oral desensitization as a useful treatment in 2-year-old children with cow's milk allergy. *Clin Exp Allergy* 41(9):1297–1304
10. Meglio P, Bartone E, Plantamura M, Arabito E, Giampietro PG (2004) A protocol for oral desensitization in children with IgE-mediated cow's milk allergy. *Allergy* 59:980–987
11. Morisset M, Moneret-Vautrin DA, Guenard L, Cuny JM, Frentz P, Hatahet R, Hanss CH, Beaudouin E, Petit N, Kanny G (2007) Oral desensitization in children with milk and egg allergies obtains recovery in a significant proportion of cases. A randomized study in 60 children with cow's milk allergy and 90 children with egg allergy. *Eur Ann Allergy Clin Immunol* 39:12–19
12. Muraro A, Roberts G, Clark A, Eigenmann PA, Halken S, Lack G, Moneret-Vautrin A, Niggemann B, Rancé F (2007) EAACI Task Force on Anaphylaxis in Children. The management of anaphylaxis in childhood: position paper of the European Academy of allergology and clinical immunology. *Allergy* 62:857–871
13. Niggemann B, Staden U, Rolinck-Werninghaus C, Beyer K (2006) Specific oral tolerance induction in food allergy. *Allergy* 61:808–811

14. Nowak-Węgrzyn A, Sampson HA (2011) Future therapies for food allergies. *J Allergy Clin Immunol* 127:558–573
15. Nowak-Węgrzyn A, Assa-Ad AH, Bahna SL, Bock SA, Sicherer SH, Teuber SS (2009) Work group report: oral food challenge testing. *J Allergy Clin Immunol* 123:S365–S383
16. Nowak-Węgrzyn A, Fiocchi A (2010) Is oral immunotherapy the cure for food allergies? *Curr Opin Allergy Clin Immunol* 10:214–219
17. Pajno GB, Caminiti L, Ruggeri P, De Luca R, Vita D, La Rosa M, Passalacqua G (2010) Oral immunotherapy for cow's milk allergy with a weekly up-dosing regimen: a randomized single-blind controlled study. *Ann Allergy Asthma Immunol* 105:376–381
18. Patriarca G, Nucera E, Roncallo C, Pollastrini E, Bartolozzi F, De Pasquale T, Buonomo A, Gasbarrini G, Di Campi C, Schiavino D (2003) Oral desensitizing treatment in food allergy: clinical and immunological results. *Aliment Pharmacol Ther* 17(3):459–465
19. Perez Machado MA, Ashwood P, Thomson MA, Latcham F, Sim R, Walker-Smith JA, Murch SH (2003) Reduced transforming growth factor- β -producing T cells in the duodenal mucosa of children with food allergy. *Eur J Immunol* 33(8):2307–2315
20. Rolinck-Werninghaus C, Staden U, Mehl A, Hamelmann E, Beyer K, Niggemann B (2005) Specific oral tolerance induction with food in children: transient or persistent effect on food allergy? *Allergy* 60:1320–1322
21. Rona RJ, Keil T, Summers C, Gislason D, Zuidmeer L, Sodergren E, Sigurdardottir ST, Lindner T, Goldhahn K, Dahlstrom J, McBride D, Madsen C (2007) The prevalence of food allergy: a meta-analysis. *J Allergy Clin Immunol* 120:638–646
22. Sampson HA, Ho DG (1997) Relationship between food-specific IgE concentrations and the risk of positive food challenges in children and adolescents. *J Allergy Clin Immunol* 100(4):444–451
23. Sampson HA (2001) Utility of food-specific IgE concentrations in predicting symptomatic food allergy. *J Allergy Clin Immunol* 107(5):891–896
24. Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson NF, Bock SA, Branum A, Brown SGA, Camargo CA, Cydulka R, Galli SJ, Gidudu J, Gruchalla RS, Harlor AD, Hepner DL, Lewis LM, Lieberman PL, Metcalfe DD, O'Connor R, Muraro A, Rudman A, Schmitt C, Scherrer D, Simons E, Thomas S, Wood JP, Decker WW (2006) Second symposium on the definition management of anaphylaxis: summary report—Second National Institute of and Infectious Disease/Food Allergy Anaphylaxis Network symposium. *J Allergy Clin Immunol* 117(4):391–397
25. Santos A, Dias A, Pinheiro JA (2010) Predictive factors for the persistence of cow's milk allergy. *Pediatr Allergy Immunol* 21:1127–1134
26. Sicherer SH, Sampson HA (2006) Food allergy. *J Allergy Clin Immunol* 117(suppl):S470–S475
27. Skripak JM, Sampson HA (2008) Towards a cure for food allergy. *Curr Opin Immunol* 20:690–696
28. Skripak JM, Matsui EC, Mudd K, Wood RA (2007) The natural history of IgE-mediated cow's milk allergy. *J Allergy Clin Immunol* 120:1172–1177
29. Skripak JM, Nash SD, Rowley H, Brereton NH, Oh S, Hamilton RG, Matsui EC, Burks AW, Wood RA (2008) A randomized, double-blind, placebo-controlled study of milk oral immunotherapy for cow's milk allergy. *J Allergy Clin Immunol* 122:1154–1160
30. Staden U, Rolinck-Werninghaus C, Brewe F, Wahn U, Niggemann B, Beyer K (2007) Specific oral tolerance induction in food allergy in children: efficacy and clinical patterns of reaction. *Allergy* 62:1261–1269
31. Strid J, Hourihane J, Kimber I (2005) Epicutaneous exposure to peanut protein prevents oral tolerance and enhances allergic sensitization. *Clin Exp Allergy* 35:757–766
32. Tang MLK (2009) Oral immunotherapy for food allergy. *Curr Allergy Asthma Rep* 9(1):43–49
33. Vetander M, Helander D, Linquist C, Hedlin G, Alfvén T, Ostblom E, Nilsson C, Lilja G, Wickman M (2011) Classification of anaphylaxis and utility of the EAACI Taskforce position paper on anaphylaxis in children. *Pediatr Allergy Immunol* 22:369–373
34. Vickery BP, Burks W (2009) Immunotherapy in the treatment of food allergy: focus on oral tolerance. *Curr Opin Allergy Clin Immunol* 9:364–370
35. Warner JO (2007) Anaphylaxis: the latest allergy epidemic. *Pediatr Allergy Immunol* 18:1–2
36. Wood RA (2008) Food-specific immunotherapy: past, present, and future. *J Allergy Clin Immunol* 121:336–337
37. Zapatero L, Alonso E, Fuentes V, Martinez MJ (2008) Oral desensitization in children with cow's milk allergy. *J Invest Allergol Clin Immunol* 18(5):389–396