

Oral desensitization in children with immunoglobulin E-mediated cow's milk allergy – follow-up at 4 yr and 8 months

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Until now, the basic treatment for food allergy has been to avoid the offending item. This approach is difficult in the case of common foods and in the case where there is a risk of severe reaction after consuming the offending food, even inadvertently. This is the follow-up of a previous study aimed at desensitizing 21 children with immunoglobulin E (IgE)-mediated cow's milk (CM) allergy. This protocol was totally or partially successful in 85% of cases, but failed in the remaining 15%. Our aims were to study the long-term effectiveness and safety of oral CM desensitization, and the prognostic value of Skin Prick Test (SPT) and specific serum CM IgE. The 21 children were called back (one dropped out). The allergic history and other information on CM intake over the last 4–5 yr were recorded. Children underwent SPT, and end-point SPT, with casein and α -lactoalbumin. Specific CM IgE was also measured. At follow-up, 14/20 children totally ($n = 13$, 65%) or partially ($n = 1$, 5%) tolerated CM. None of the recalled children reported use of emergency care. SPT positivity to casein and/or α -lactoalbumin decreased significantly ($p < 0.01$), and all the negative SPT referred to the tolerant children. Cutaneous sensitivity to both casein and α -lactoalbumin (end-point SPT) significantly decreased after the 6-month desensitization period of the previous study ($p < 0.001$), but did not decrease significantly at follow-up. A significant reduction of serum-specific CM IgE was also observed ($p < 0.05$). Clinical tolerance induced by oral CM desensitization persists in time. Negativization of SPT and reduction of specific CM IgE could be considered prognostic indicators of CM tolerance. Oral CM desensitization seems to be a promising method to treat CM food allergy. This protocol is time-consuming but offers the advantage that it can be performed at home. This methodology must only be used by trained staff.

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Definitive treatment of food allergy is still controversial. Although the debate is open concerning future approaches (1, 2), until now the basic treatment for adverse reactions to foods has mainly been to avoid the offending item (3–5). This approach is difficult in the case of very common foods, and sometimes elimination diets can induce psychological problems. In cases where a certain food could induce a severe

allergic reaction, the child and the family are frequently worried about the risk of consuming even small amounts of the offending food inadvertently (6). Moreover, while many children outgrow their food allergies, generally speaking, the more persistent the food allergy is over time, the lesser the probability of recovering spontaneously, at least in the short term (3, 7).

For these reasons, it may be advisable to try to induce oral clinical tolerance to the offending food – both in the case where oral tolerance could never have been reached (or where it would have taken a long time to reach) and when risk of severe or threatening life reactions exists.

As previous experiences of oral desensitization with CM have appeared to be successful in some cases (8–10), 5 yr ago we decided to adopt our desensitization protocol in 21 children with immunoglobulin E (IgE)-mediated CM allergy (CMA) to induce oral tolerance to CM. Our protocol was totally or partially successful in some 86% of the cases (18/21 children), but failed in the remaining 14% of the cases (3/21 children) (11).

In the meantime, other successful studies have been performed on individual or small groups of children to desensitize them to CM (12, 13) or to other foods (12–15), but until now the fate of the children who artificially acquired clinical tolerance to CM was not known because of the lack of long-term follow-up studies of an homogeneous group of patients.

Aims

This study concerns the follow-up after 4 yr and 8 months to our previous study (11) aimed at desensitizing a group of children with severe IgE-mediated CMA over a period of 6 months, by introducing increased daily doses of CM.

The objectives were to study – (i) the long-term effectiveness of oral desensitization to CM; (ii) the long-term safety of our desensitization protocol; (iii) the change in cutaneous sensitivity to CM by means of SPT and end-point SPT; (iv) the course of the specific serum CM IgE; and (v) the prognostic value of SPT, end-point SPT, and the specific serum CM IgE.

Patients, materials and methods

All the children who had participated in the previous study were called back after an average of 4 yr and 8 months (time span ranging from 4 to 5 yr and 1 month) between February and July 2004. The length of the follow-up period was calculated from the beginning of desensitization (administration of first drop of diluted CM) to the follow-up visit (Table 1). The desensitization protocol lasted for a mean period of 201 days (range: 183–234 days) (11).

During the final visit at the end of the desensitization protocol, we advised parents not to discontinue the free daily intake of CM and/or CM by-products, (given *ad libitum*) to maintain the effect of oral desensitization. Moreover, as a

precaution, previously we had stressed the importance of always having emergency therapy at hand. Since the previous study, parents had also been given a diary card in which to record possible reactions.

We examined 20 of the 21 children who had participated in the desensitization protocol (95%). Only in one case was it impossible to contact the family (5% dropout rate).

At the follow-up visit, on the basis of a structured interview, a clinical history detailing sex, age, family and personal history of allergies, and symptoms over the last 4–5 yr was recorded. Moreover, the parents were asked whether the totally or partially desensitized children were still consuming CM, and the amount of daily CM intake; data on safety and adverse reactions to CM were also elicited. In 14/20 children answers were given by both parents, and in 6/20 children only by mothers.

Skin Prick Test

All the children again underwent SPT with common, commercial inhalant allergens (*Dermaphagoides pteronyssinus*, *Lolium perenne*, *Parietaria officinalis*, *Olea europea*, *Alternaria tenuis*, cat dander) and with commercial food allergens (casein, α -lactoalbumin, egg white, soy, wheat, and cod) (Lofarma, Milan, Italy). SPT were performed as previously described (11).

End-point SPT with casein and α -lactoalbumin extracts were also performed once more. On a different day from that of the standard SPT, two series of SPT with scalar amounts of casein and α -lactoalbumin extracts were performed, starting with 1:20 w/v of casein and α -lactoalbumin. The casein end-point SPT were performed on the right forearm, and the α -lactoalbumin test on the left, applying drops of extract diluted 1:1, 1:10, 1:100, 1:1.000, and 1:10.000. As in the case of the standard SPT, these reactions were read at 15 min, and the mean of the sum of the reactions compared.

Double-blind placebo-controlled food challenge test (DBPCFCT)

Double-blind placebo-controlled food challenge test with CM and placebo were proposed to the three children (#19, #20, and #21) who previously failed oral desensitization, but it was carried out only in patient #21 with the same method as in the previous study (11). DBPCFCT was not performed in patient #20 because of a recent convincing history (vomiting and throat pruritus) after inadvertent ingestion of CM. Parents of patient #19 refused to do it.

Oral desensitization in children with IgE-mediated CM allergy follow-up

Table 1. Follow-up outcome after cow's milk (CM) desensitization

Patient		Age at the start of CM desensitization in the previous study (11) (yr, months)	Outcome of CM desensitization in the previous study (11)	Follow-up period (yr, months)	Outcome of follow-up
#1	ChF	7, 3/12	*	4	Tolerates CM
#2	DAA	6, 1/12	*	4, 2/12	Tolerates CM
#3	DGP	6, 5/12	*	4, 3/12	Tolerates CM
#4	GF	8, 1/12	*	4, 4/12	Tolerates CM (CM reduced to 50 ml/day as pediatrician believed rhinitis depended on CM. Afterwards stopped consuming CM. Now eats CM by-products)
#5	IA	8, 6/12	*	4, 6/12	Tolerates CM
#6	LPD	10, 4/12	*	4, 6/12	Tolerates CM
#7	PerM	7, 10/12	*	4, 7/12	Tolerates CM (he does not enjoy CM, but is on a free diet)
#8	PetM	5, 6/12	*	4, 7/12	Tolerates CM (he does not enjoy CM, but is on a free diet)
#9	CF	5, 3/12	**	4, 7/12	Because of viral diarrhea, stopped CM intake for 1 month. When he began consuming 100 ml CM again, urticaria and asthma resulted. Stopped taking CM and experiences pruritus with CM by-products
#10	CS	5, 6/12	**	4, 8/12	Tolerates CM partially (diarrhea intervenes with >60 ml of CM. He tolerates <60 ml of CM per day)
#11	ML	10, 2/12	**	dropout	–
#12	PI	7, 3/12	**	4, 9/12	Tolerates CM
#13	MR	10	**	4, 9/12	Tolerates CM
#14	RR	8, 7/12	**	4, 10/12	Tolerates CM
#15	TS	6	**	4, 11/12	Tolerates CM
#16	DOA	6, 7/12	***	4, 12/12	Tolerates CM (he continued to consume 47 ml/day of CM for 4 months, then suspended CM, occasionally eating cheese. One year later, underwent another oral food challenge test that was negative. Since then, consumes CM freely)
#17	PM	7, 6/12	***	4, 12/12	Continued drinking 45 ml of CM for 6 months. Above this quantity, lip edema and oral itch resulted. Because of mother's anxiety and depression was put back on a CM-free diet
#18	VS	8, 3/12	***	5	Interrupted daily assumption of CM because mother wanted him to drink CM freely, not only low amounts
#19	DV	5, 10/12	****	5	Does not eat CM
#20	GS	6, 11/12	****	5, 1/12	Does not eat CM
#21	PD	6, 1/12	****	5, 1/12	Does not eat CM

Outcome of previous CM desensitization (11):

*tolerated 200 ml of whole CM per day.

**tolerated 200 ml of whole CM per day (presented some symptoms which occurred in a short time after ingestion of CM which persisted for less than 2 h).

***tolerated between 40 and 80 ml of whole CM per day.

****oral CM desensitization failed (immediate onset of allergic symptoms after a few doses).

Blood samples

Peripheral, venous blood samples were collected and the serum samples stored at -20°C . For each serum sample, the total IgE and the specific IgE for α -lactoalbumin and casein were determined by REAST (Realtest[®]-Total-IgE and Realtest[®]-Specific IgE, Lofarma). As described previously (11), the REAST values are comparable with the RAST ones (16). Sideremia and hemochrome to check anemia were also tested.

Feces samples

Hidden blood in the feces was tested twice consecutively for (Hema Screen, Immunostics, Inc., Ocean, NJ, USA).

Informed consent from each family was obtained.

Statistical analysis

Follow-up measurements were compared with those at the end of desensitization protocol (the 'post' data of the previous study (11) – to evaluate the changes in the patients who completed the desensitization protocol) and to the measurements at the start of the desensitization protocol (the 'pre' data of the previous study (11) – to assess the evolution, in an intention-to-treat analysis).

These comparisons were performed by means of the McNemar test for SPT, and the Wilcoxon matched pairs signed ranks test for paired data

for the other parameters. REAST values were previously log-transformed to reduce the weight of outliers, because of the Wilcoxon paired test sensitivity to such transformations.

Results

Family and personal history

Sixteen of the 20 children (80%) had a positive family history for atopic diseases (previous data 16/21, 76%); 16/20 children (80%) had had atopic dermatitis in the past (previous data 16/21, 76%); 4/20 children (15%) suffered from conjunctivitis (previous data 8/21, 39%); 13/20 children (65%) suffered from allergic rhinitis (previous data 17/21, 81%); and 7/20 children (35%) suffered from asthma (previous data 15/21, 71%). With the exception of asthma ($p < 0.025$), the other parameters did not differ significantly.

Outcome of the oral desensitization follow-up

Overall, at the end of the previous study 18/21 children totally ($n = 15$) or partially ($n = 3$) tolerated CM. At follow-up, 14/20 children totally ($n = 13$) or partially ($n = 1$) tolerated CM. The only dropout (patient #11) belonged to the group of children who were previously totally desensitized. In particular, 9/14 of these tolerant children (patients #1, #2, #3, #5, #6, #12, #13, #14, and #15) had been consuming CM (generally, one cup at breakfast, that is to say about 250 ml/die) and derivatives freely, and without interruption as the desensitization protocol was terminated. Another child in this group (patient #4) reduced CM intake to 50 ml/day 4 months after the end of the protocol as his pediatrician believed his rhinitis depended on the consumption of CM. His mother decided not to administer CM any more for fear that it could be harmful, but the child now daily consumes Parmesan cheese and other CM by-products without symptoms. Two other children in this group (patients #7 and #8) are on a free diet, but do not enjoy CM although they occasionally drink it and eat cheese and other by-products without symptoms. Patient #10 developed mild diarrhea after a symptom-free period of approximately 4 months. He, therefore, stopped consuming whole CM again, but continued eating CM by-products without symptoms. He tried drinking CM at home and can now tolerate the maximum dosage of 60 ml/day of whole CM. If he consumes more than 60 ml of whole CM per day, diarrhea results. The last child of this group (patient #16) who could previously tolerate up to

47 ml of CM continued to consume this amount of CM for 4 months. He then stopped drinking CM, occasionally eating cheese. Around 1 yr later, he underwent another oral food challenge test that was negative. Since then, he has been consuming CM freely.

Six out of 20 children could not tolerate CM at follow-up. In particular, one child (patient #9) continued to consume CM on a regular basis for 6 months after the desensitization period. As a result of viral diarrhea, he stopped consuming it for approximately 1 month. After that, he went straight back onto 100 ml of CM, but urticaria and asthma resulted. Therefore, he stopped taking CM, and now when he occasionally eats Parmesan cheese, he experiences oral itch. He has not tried to drink CM since. The second child (patient #17) continued drinking small amounts (45 ml) of CM for about 6 months. Every time he tried to increase this intake, slight lip edema and oral itch resulted. This made his mother very anxious and depressed, which is why she put her son on a CM-free diet again, so as to have more control over her child's problem. This child is still on a CM-free diet. The third child (patient #18) interrupted daily consumption of CM because his mother wanted him to consume CM freely given that, in his specific case, there was no risk of small occasional doses of CM provoking a severe reaction (Table 1).

Safety data and adverse reaction to CM

None of the children reported the use of adrenaline or required other emergency care during the follow-up period. The symptoms reported by some children (Table 1) were controlled by oral antihistaminics.

Skin Prick Test

SPT with commercial common inhalant allergens tested positive for *D. pteronyssinus* (65%, previously 61.1%), *L. perenne* (75%, previously 71.4%), *P. officinalis* (45%, previously 47.6%), *O. europea* (45%, previously 42.8%), *A. alternata* (15% previously 19%), cat dander (40% previously 23.8%), egg white (45%, previously 76.2%), cod (20%, previously 23.8%), wheat (5%, previously 0%), and soy (10%, previously 0%). Considering SPT positivity to casein and/or α -lactalbumin together (Table 2), 21/21 children tested positive when they entered the study (pre) and 16/18 children at the end of the 6 month period (post) of oral desensitization, and 14/20 children at the follow-up visit. The

Table 2. Outcome of casein and β -lactoglobulin skin prick test (SPT), end-point SPT, and REAST values at the start of the desensitization protocol (previous study, Pre), at the end of the 6-month protocol period (previous study, Post), and at the follow-up visit (F-up)

Patient	Casein and/or α -lactalbumin SPT			Casein end-point SPT (mm)			α -Lactalbumin end-point SPT (mm)			Casein REAST (kU/ml)			α -Lactalbumin REAST (kU/ml)			Tolerates cow's milk (CM)
	Pre	Post	F-up	Pre	Post	F-up	Pre	Post	F-up	Pre	Post	F-up	Pre	Post	F-up	
#1	ChF	+	–	32	15	5	17	5	5	0.72	0.48	0.60	0.58	9.69	10.08	Yes
#2	DAA	+	–	27	17	10	19	23	10	0.10	0.00	0.00	0.90	0.80	0.00	Yes
#3	DGP	+	–	26	17	7	23	13	7	0.98	0.56	8.83	4.19	4.30	8.27	Yes
#4	GF	+	+	35	15	15	40	29	24	1.50	1.40	0.00	4.05	3.10	0.39	Yes
#5	IA	+	+	24	8	6	30.5	22	21	0.00	0.00	0.00	8.40	8.40	3.80	Yes
#6	LPD	+	–	24	16	7	45	21	7	1.50	0.61	0.10	5.30	2.92	0.10	Yes
#7	PerM	+	–	18	5	10	28	12	10	0.00	0.15	0.00	1.19	1.36	0.00	Yes
#8	PerM	+	+	33	20	20	34	25	15	3.47	2.30	1.52	147.00	79.10	75.00	Yes
#9	CF	+	+	50	24	31	40	19	38	2.64	1.61	0.00	4.21	4.77	0.60	No
#10	CS	+	+	24	n.d.	6	37	n.d.	5	0.50	0.62	0.60	0.37	0.56	0.55	Yes
#11	ML	+	d.o.	25	8	d.o.	49	25	d.o.	0.00	0.00	n.d.	4.90	3.30	n.d.	d.o.
#12	PI	+	+	23	6	13	32	14	5	0.63	0.00	0.00	0.50	1.00	1.02	Yes
#13	MR	+	+	25	11	12	39	15	11	0.00	0.40	0.05	0.00	1.20	0.44	Yes
#14	RR	+	+	37	15	15	20	5	12	3.46	1.96	0.36	1.38	0.72	0.17	Yes
#15	TS	+	–	32	23	8	34	5	7	3.30	n.d.	0.40	1.50	n.d.	0.47	Yes
#16	DOA	+	+	24	8	12	21	15	6	0.49	0.00	0.00	15.30	4.90	0.00	Yes
#17	PM	+	+	24	22	27	42	25	49	1.03	2.96	3.78	110.00	85.00	24.40	No
#18	VS	+	+	33	25	26	21	15	21	5.80	3.15	3.60	0.00	0.00	0.02	No
#19	DV	+	n.d.	16	n.d.	18	17	n.d.	17	9.30	n.d.	4.90	43.20	n.d.	35.00	No
#20	GS	+	n.d.	33	n.d.	25	36	n.d.	23	14.40	n.d.	0.00	14.20	n.d.	2.32	No
#21	PD	+	n.d.	43	n.d.	24	51	n.d.	52	10.40	10.92	16.50	41.77	56.10	49.50	No
		Positive SPT		29 (± 7)	15 (± 6)	15 (± 8)	31 (± 10)	16 (± 7)	17 (± 14)	1.8 (± 2.7)	1.5 (± 2.6)	21.1 (± 4.4)	19.4 (± 41.3)	14.8 (± 27.6)	10.5 (± 21.0)	Average ($\pm$ SD)
				26	15	13	34	15	12	1.0	0.6	0.23	4.2	3.2	0.6	Median
				21/21	16/18	14/20	18–50	5–29	5–49	0–10.4	0–10.92	0–16.5	0–147	0–85	0–75	Range
Pre vs. Post	n.s. ($p = 0.5$)*			Significant ($p < 0.001$)*			Significant ($p < 0.001$)*			n.s. ($p = 0.107$)*			n.s. ($p = 0.571$)*			
Post vs. F-up	n.s. ($p = 0.219$)†			n.s. ($p = 0.421$)‡			n.s. ($p = 0.426$)‡			n.s. ($p = 0.345$)§			Significant ($p = 0.006$)§			
Pre vs. F-up	Significant ($p < 0.031$)†			Significant ($p < 0.001$)‡			Significant ($p < 0.001$)‡			Significant ($p = 0.043$)§			Significant ($p = 0.023$)§			

SPT were considered as positive if wheals were 3 mm or more in diameter, and at least 3 mm more than the negative control.

In the previous study (11), children #1–#15 tolerated the daily intake of 200 ml of CM, children #16–#18 tolerated 40–80 ml/day of undiluted CM, and children #19–#21 failed the desensitization.

n.s. = not significant.

d.o. = dropped out.

n.d. = not done.

*see reference 11 for statistical methods.

†with the McNemar test.

‡with the Wilcoxon matched-pairs signed-ranks test.

§with the Wilcoxon matched-pairs signed-ranks test (after logarithmic transformation).

three children who failed desensitization were not tested again. The differences were not significant in pre vs. post, and post vs. follow-up SPT, but were significant in pre vs. follow-up SPT ($p = 0.031$). All the negative SPT belonged to the group who were still tolerant at follow-up (6/14 children). None of the six intolerant children had negative SPT to casein or α -lactalbumin at follow-up.

End-point SPT with casein and α -lactalbumin

Cutaneous sensitivity to both casein and α -lactalbumin significantly decreased after the 6 month desensitization period of the previous study (11) (pre vs. post, $p < 0.001$). The difference between values at the start of desensitization and the follow-up visit (pre vs. follow-up) remained significant ($p < 0.001$). There was no significant difference between the post vs. follow-up end-point SPT to both casein and α -lactalbumin (Table 2).

Double-blind placebo-controlled food challenge test

The last three children who were not able to tolerate CM previously (patients #19, #20, and #21) had never tried drinking CM in the interim period with the exception of patient #20 who had a reaction after inadvertent ingestion of CM. The only DBPCFCT (patient #19) with CM turned out to be positive. The test with placebo was negative. Moreover, this patient underwent a new desensitization protocol but it failed again (data not shown).

Specific IgE for Casein and α -lactalbumin (REAST)

The differences between casein and α -lactalbumin specific IgE (REAST) pre and post oral desensitization were not significant (11). The differences between the casein specific IgE (REAST) at the post and follow-up visit were not significant, but the differences between α -lactalbumin specific IgE (REAST) at the post and follow-up visit were significant ($p = 0.007$). The differences between specific IgE at the pre and the follow-up visit were significant for both casein ($p = 0.043$) and α -lactalbumin ($p = 0.023$) (Table 2).

Blood and feces samples

All the hemochrome and sideremia values were normal and there was no trace of hidden blood in the feces of any child.

Discussion

This is the follow-up of our study performed in 21 children with severe IgE-mediated, CMA (11). To our knowledge, this is the first long-term follow-up (after 4 yr and 8 months), for a homogeneous group of children who underwent a protocol for oral desensitization to CM. Overall, only one child (patient #11) dropped out. The following remarks do not take this child into account.

Persistence of the oral desensitization effect

Overall, at the end of the previous study, 18/21 children totally ($n = 15$) or partially ($n = 3$) tolerated CM, and at follow-up 14/20 children still totally ($n = 13$) or partially ($n = 1$) tolerated CM, thus indicating a substantial persistence of the oral desensitization effect. Only a few studies have reported the long-term natural history of CMA (17). The total recovery from CMA was of 56% at age 1 (18), 65 to 77% at 2 (18, 19), 87% at 3 (18), 92% at 5, 92% at 10 (20), and 97% at 15 (20). These cannot be considered as absolute results because of differences in patient characteristics, age at entry into the studies, study design, diagnostic criteria, and duration of the follow-up period. Moreover, the older the child upon entry into the study, the lower the probability of he or she developing tolerance to CM (17). In our opinion, we have changed the natural history of CMA in most of our patients by anticipating the natural time of clinical tolerance. Possibly, we allowed some of them to gain tolerance that would never have been reached spontaneously. Nevertheless, we have to remember the main objective of our protocol was to improve the quality of life of these children by reducing the risk of (severe) reactions after consuming CM, even inadvertently.

Effect of stopping consumption of CM after oral desensitization

One child (patient #9) interrupted the consumption of CM for 1 month, and then went straight back onto 100 ml of CM, experiencing urticaria and asthma. This poses the problem whether oral desensitization-induced food tolerance is persistent or can decline after stopping regular consumption of the offending food. This reaction was not correlated with a high REAST class (Table 2), so we believe that, at least in this particular case, specific IgE values would not have been useful to predict the reaction.

In this context, Rolinck-Werninghaus et al. (12) recently reported successful desensitization to CM in one child, and to hens' egg in two children. The patient desensitized to CM in 37 wk continued the maintenance dose for 27 wk and then received a strict secondary elimination diet for 2 months prior to a follow-up DBPCFC, during which he experienced acute urticaria within 15 min at a cumulative dose of 50 ml CM. Orally desensitized again, he re-acquired tolerance within 8 wk. A similar phenomenon occurred even in the egg-desensitized patients. As a consequence, the authors speculate that tolerance induced by oral desensitization is not of a persistent nature, but increases the threshold dose necessary to elicit allergic symptoms, resulting in clinical tolerance. In the absence of daily allergen intake, the threshold dose is likely to decrease again so.

In consideration of the low number of cases we cannot exclude that others may reach definitive oral tolerance, depending on the clinical and immunologic characteristics of the patient. We are aware that limited information is available on the dosage intervals needed in the maintenance phase to preserve the acquired tolerance; however, the studies of Patriarca et al. (9) suggest the frequency could even be three times per week. Whatever the case, we empirically maintain that the more severe the CMA, the more regular and frequent the food intake should be during the maintenance period.

Long-term safety

Safety is an important issue, and it concerns any kind of desensitization; indeed, we think if desensitization were absolutely safe, the treatment would be more widespread. During this follow-up, none of the children needed to use adrenaline, and possible minor symptoms were controlled by oral antihistaminics. In practice, we were only concerned about the child (patient #9) previously described, and for this we recommend consumption of CM on a regular basis after the end of the oral desensitization. Possible predictive indices should be identified, but until they are, re-introduction of CM after a long diet period should be performed on a controlled set (12).

Psychological problems and expectations

For fear of severe reactions caused by attempts to increase the CM dose higher than the 45 ml tolerated, patient #17's mother fell into depression. On the contrary, patient #18's mother interrupted daily administration of CM because she wanted

to give her son CM freely, instead of keeping to a lower (but safe) dose (Table 1). Basically, these two children were partially desensitized because the maximum amount of CM tolerated had been identified, thus minimizing or eliminating possible severe reactions as a result of accidental or unnoticed introduction of low quantities of CM. We, therefore, maintain that great efforts must be made to depict the possible scenarios of this kind of protocol, which in our case lasts 6 months, but is intended to continue beyond this period. So, possible psychological problems and/or parents' expectations have to be taken into account and can sometimes lead to a decision not to undergo the desensitization protocol.

Course of the specific CM IgE and prognostic factors

Interestingly, we noted that SPT to casein and/or α -lactoalbumin became negative only in the children who still tolerated CM at follow-up. None of the non-tolerating children switched from positive to negative SPT (Table 2). We speculate that this switch could be considered a sign of tolerance acquisition. This tendency was also supported by the significant decrease of both casein and α -lactoalbumin end-point SPT during the desensitization period, although they remained unchanged during the follow-up period (Table 2).

Moreover, we observed this progression with the REAST values also, even if such a significance was stronger for α -lactoalbumin (Table 2). This coincides with the study of Vanto et al. (21) who showed that in children aged 4, both SPT and serum specific IgE were useful prognostic indicators of the development of tolerance to CM.

Conclusions

Oral food desensitization seems to be a promising method to treat CMA. Our follow-up after 4 yr and 8 months concerns 20/21 children studied previously and indicates that overall, 14/17 previously totally or partially desensitized children are still consuming CM or CM by-products freely ($n = 13$) or partially ($n = 1$).

We confirm that this protocol is time-consuming, but offers the advantage that it can be performed at home. In our opinion, the protocol has been an overall success and is quite safe, although some children needed to be followed closely even after the end of the protocol.

It is possible that in some cases the clinical tolerance cannot be definitive but lasts as long as

the offending food is regularly consumed. In general, it is difficult to evaluate whether the good prognosis is due just to the natural course of CMA or to the treatment/desensitization performed 4–5 yr previously, but on the contrary, we think that in most of our children we have at least anticipated the natural time of clinical tolerance so ameliorating their quality of life in terms of reduction of risk and/or anxiety. However, we are aware that definitive answers can only be given from prospective randomized studies.

We maintain that standardization of this method is needed and further studies are warranted to better characterize patients who can be good candidates for oral desensitization. Moreover, immunological characterization of patients should be performed to understand the mechanisms that regulate tolerance acquisition and, possibly, to monitor oral tolerance induction.

Negativization of SPT to casein and/or α -lactalbumin, and the reduction of the serum-specific IgE could be considered as prognostic indicators of the development of tolerance to CM.

Finally, we stress that this methodology must only be used by appropriately trained staff.

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