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ORIGINAL ARTICLE

Oral desensitization as a useful treatment in 2-year-old children with cow's milk allergy

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Summary

Background Limited published evidence shows oral desensitization to be a potential intervention option for cow's milk protein (CMPs) allergy.

Objective The aim of this study was to evaluate the safety and efficacy of oral desensitization in 2-year-old children with cow's milk allergy, as a treatment alternative to elimination diet.

Methods A total of 60 children aged 24–36 months with IgE-mediated allergy to CMPs were included in this multi-center study and were randomized into two groups. Thirty children (group A: treatment group) began oral desensitization immediately, whereas the remaining 30 (group B: control group) were kept on a milk-free diet and followed-up for 1 year.

Results After 1-year follow-up period, 90% of the children in group A had become completely tolerant vs. 23% of the children in group B. In group A, cow's milk skin reactivity and serum-specific IgE to milk and casein decreased significantly from the initial assessment, whereas group B showed no significant change after 1 year of follow-up. Twenty-four patients (80%) developed some reaction during the treatment period: 14 children developed moderate reaction (47%) and 10 mild reaction (33%). The most common manifestations were urticaria-angioedema, followed by cough.

Conclusions and Clinical Relevance In this study, oral desensitization was found to be effective in a significant percentage of 2-year-old children with cow's milk allergy. Oral desensitization appears to be efficacious as an alternative to elimination diet in the treatment of 2-year-old children with cow's milk allergy. The side-effect profile appears acceptable but requires further study.

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Introduction

Allergy to cow's milk proteins (CMPs) is the first food allergy to manifest in children [1, 2]. The current options for the management of food allergy are based on allergen avoidance, until the development of tolerance. However, in some very common foods such as cow's milk, this approach is difficult to apply. Moreover, not all subjects reach tolerance. In some cases the problem persists for years, and the longer symptomatic sensitization persists, the smaller the chances for resolution of the disorder [3–6].

The difficulty of strict avoidance of the causal food, and particularly the risk of reaction, have led to research into

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developing new therapeutic options for the control of food allergy. A number of treatments are currently being evaluated (subcutaneous immunotherapy [7], administration of anti-IgE [8], specific oral tolerance induction or oral desensitization [9], sublingual immunotherapy [10]) with the aim of shortening the time to tolerance, or at least of raising the reaction threshold dose in order to avoid the risk of serious reaction due to accidental exposure.

Although limited, published evidence shows oral desensitization to be a possible intervention [11–17]. Previous studies have been carried out in children over 5 years of age.

The major objective of this study was to assess the safety and efficacy of an oral desensitization protocol in 2-year-old children with allergy to CMPs, as a treatment alternative to elimination diet (diet free of milk and derivates). The age of patients was set at 2 years to avoid a confusing effect due to age (age has an effect in terms of enhancing the possibility of developing tolerance). We would like to prove that oral desensitization could be an alternative to elimination diet for food allergy more than a compassionate procedure.

Patients and methods

A randomized, controlled, parallel-group, multi-centre trial was conducted. The oral desensitization protocol is provided in Table 1. The study was carried out in the Paediatric Allergology Units of Spanish Hospitals (see author's list).

All the dose increases were administered under supervision at the hospital and the doses were subsequently maintained at home (twice a day), with elevation once a week at the research units. Home diary forms were provided to record the dose, date and time taken, symptoms occurring after the dose or any other time, and medications taken each day. None of the patients received preventive pharmacological treatment.

Table 1. Oral desensitization protocol

	Milk (dilution)	Dose (mL)
Day 1	1/100	1
In hospital		2
Doses hourly		4
		8
	1/10	1.6
Day 2	1/10	1.6
In hospital		3.2
Doses		6
hourly		12
	Pure	2.5
Dose maintained at home, with elevation	Pure	4
once a week in hospital		6
Total 16 weeks		8
		10
		12
		15
		20
		25
		30
		40
		50
		75
		100
		125
		150
		200

Enrolment of patients and inclusion criteria

Consecutive patients were included according to the following criteria:

1. Infants aged from 24 to 36 months.
2. IgE-mediated allergy to CMPs meeting all the following diagnostic criteria:
- Immediate-type clinical manifestations, skin (urticaria, angioedema and/or erythema), digestive (acute vomiting and/or diarrhoea) or respiratory (bronchospasm and/or rhinitis) involvement in the first two hours after cow's milk ingestion.
- Skin test readings ≥ 3 mm and specific IgE levels > 0.35 kU/L for whole cow's milk or any isolated CMPs (casein, α-lactoalbumin, β-lactoglobulin).
3. Persistence of CMP allergy in the 4 weeks before tolerance induction, based on the following criteria:
- SPT readings ≥ 3 mm and specific IgE levels [CAP-fluorescent-enzyme immunoassay (FEIA)] > 0.35 kU/L for whole cow's milk or any isolated CMPs (casein, α-lactoalbumin, β-lactoglobulin).
- Double-blind placebo-controlled food challenge (DBPCFC) positive to cow's milk.
4. Written informed consent from the parents.

Exclusion criteria

1. Clinical manifestations of anaphylactic shock after the ingestion of cow's milk.
2. Non-IgE-mediated or non-immunological adverse reactions to cow's milk.
3. Malignant or immunopathological diseases and/or severe primary or secondary immune deficiencies.
4. Patients receiving immunosuppressor therapy.
5. Patients receiving β-blockers (including topical formulations).
6. Associated diseases contraindicating the use of epinephrine: cardiovascular disease or severe hypertension.

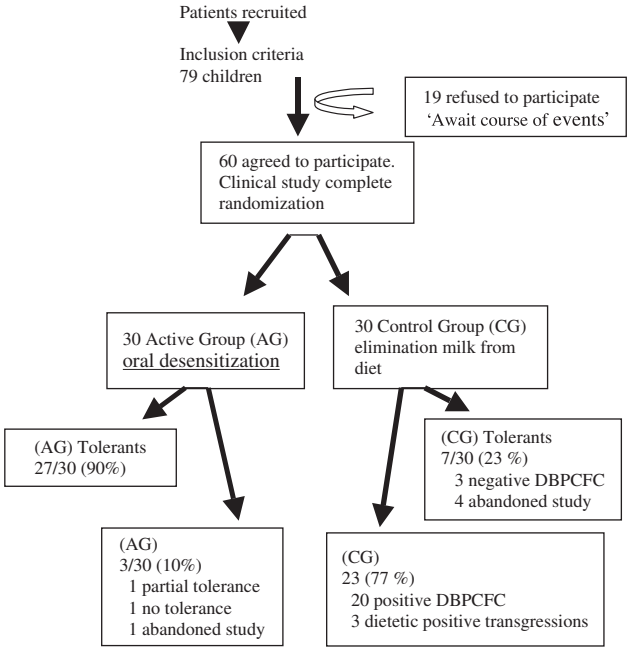

Fig. 1. Schematic representation of the study design and results after 12 months of follow-up. DBPCFC, double-blind placebo-controlled food challenge.

The children enroled were randomized to two groups: active group (AG) started oral desensitization immediately after DBPCFC and control group (CG) maintained a milk-free diet for 1 year (Fig. 1).

Skin prick tests

Skin prick tests (SPTs) were performed with whole cow's milk (10 mg/mL) (ALK-Abelló, Madrid, Spain) and with isolated CMPs: casein (10 mg/mL) (LETI, Barcelona, Spain), α-lactoalbumin (5 mg/mL) and β-lactoglobulin (5 mg/mL) (DIATER, Madrid, Spain), following standardized methodology [18].

End-point SPTs titration technique with dilutions of fresh whole cow's milk in physiological saline, were made. The most dilute dilution with a weal at least as large as that elicited by the histamine control was considered the threshold.

Laboratory studies

Serum determinations of specific IgE antibodies to cow's milk, casein, α-lactoalbumin and β-lactoglobulin were assayed with the CAP-FEIA technique (Phadia, Uppsala, Sweden). Test positivity was considered for values above 0.35 kU/L.

Challenge test

DBPCFC testing to cow's milk was carried out, following the indications of the European Academy of Allergology and Clinical Immunology [19]. Soya formula was used as placebo. Cow's milk and soya formula were masked in a mash of potato and olive oil.

Study variables

1. The primary study variable was oral tolerance of CMPs 1 year after the start of the trial. This is a qualitative variable with three categories: total tolerance (200 mL of cow's milk); partial tolerance (20–200 mL); and no tolerance (< 20 mL). Only patients presenting total tolerance were regarded as being tolerant.
2. Secondary variables were: skin sensitivity to CMPs and threshold dose in DBPCFC, total IgE before desensitization, and specific IgE against milk and casein.
3. Adverse reactions were studied. Severity of reaction was classified by consensus among all the investigators, as follows:

- *Mild*: Localized erythema or urticaria, vomiting, rhinitis, and conjunctivitis.
- *Moderate*: Generalized urticaria, facial angioedema, cough and mild bronchospasm.
- *Severe*: Severe bronchospasm, breathing difficulties with inspiratory stridor, hypotension and anaphylactic shock.

Patient follow-up

AG patients who achieved total tolerance continued drinking a dose of 200 mL of cow's milk once a day, every day, and cow's milk and dairy products without restrictions. Telephone follow-up of AG was done 2 weeks and 6 months after reaching the maximum tolerated dose. Parents had precise instructions to consult the research units if children had any symptoms with the ingestion of cow's milk.

One year after baseline provocation testing, the skin tests and specific IgE determinations were repeated and DBPCFC carried out in CG and AG patients in whom oral desensitization had failed.

At the end of the study, oral desensitization was offered to the CG patients who had not achieved tolerance.

Statistical analysis

Taking into account that in a previous study, only 30% of children aged 24–36 months with persistent CMP allergy developed tolerance after 12 months [3], and that the aim was to detect a 40% difference with the desensitization protocol, for a two-sided α-error of 0.05, a potency (1-β) of 0.80 and a dropout rate of 10%, the calculated sample size was 52 subjects (26 in each group). To provide for patient losses in excess of 10%, the number of individuals in each group was increased to 30.

Patients were recruited consecutively. Assignment to AG or CG was made on a centralized simple random basis (random numbers table), calling the principal investigator.

The statistical analysis was performed on an intention-to-treat (ITT) basis. All patients abandoning the study before completing the oral desensitization protocol were taken to be non-responders, regardless of the time or reason for withdrawal.

Estimation of the association between qualitative variables was based on the χ^2-test, Fisher's exact test or McNemar's test for independent or paired data, as applicable. Continuous variables with a normal distribution were compared by parametric analysis of variance (ANOVA) or the Student's *t*-test for paired or independent samples. Non-parametric Wilcoxon's test or the Mann–Whitney *U*-test were used in non-normal distribution. A significance level of $\alpha = 0.05$ was established.

A binary logistic regression model was developed to evaluate the possible intervention (oral desensitization protocol) effect confounding variables. A variable was considered as having a confounding effect if it was able to change oral desensitization crude odds ratio $> 10\%$.

Analysis of the tolerability/safety of the oral desensitization protocol and exclusion diet included the distribution of frequencies of all the events, adverse reactions and dropouts.

Consensus and ethics committee approval

Informed consent was obtained from all parents. The ethics committee of Valencia University General Hospital (Valencia, Spain) approved the study.

Clinical trial registered at Clinicaltrials.gov with ID: NCT01199484.

Results

Between February 2006 and February 2008, a total of 79 patients were recruited. For the 19 patients who refused to participate, the reason given was to 'await the course of events' (Fig. 1). A total of 60 patients were finally included: 30 patients were assigned to AG and 30 to CG. Table 2 shows clinical symptoms after milk ingestion and the results of the challenge. The patient groups were homogeneous as regards the variables of interest (Table 3).

In the AG, 27 patients (90%) reached the tolerance dose of 200 mL, and all remained tolerant after 12 months of follow-up. The DBPCFC was not done at the end of the study in these patients since they were taking doses of 200 mL of cow's milk once a day, every day, and cow's milk and dairy products without restrictions with good tolerance.

One patient abandoned the study as a result of moving house before reaching the maximum dose. Another patient abandoned the study due to poor tolerance of the desensitization protocol (urticaria, rhinoconjunctivitis, cough and wheezing on reaching the 2.5 mL dose), while partial tolerance was achieved in another patient (35 mL of milk) (Fig. 1).

In the CG, after 12 months of follow-up, DBPCFC was performed in 23 children and proved positive in 20. The test was not carried out in seven subjects: three infants had suffered an immediate allergic reaction following accidental ingestion in the month before the test; in three

Table 2. Clinical symptoms with milk

	Clinical history ($n = 60$)	DBPCFC ($n = 60$)	OD ($n = 30$)
Cutaneous symptoms (erythema/urticaria/angioedema)	58 (97%)	57 (95%)	20 (67%)
Gastrointestinal symptoms (vomiting/acute diarrhoea)	35 (58%)	15 (25%)	9 (30%)
Respiratory symptoms (rhinitis/conjunctivitis/cough/disphonia/bronchospam)	11 (18%)	21 (35%)	15 (50%)
Associated symptoms (cutaneous/gastrointestinal/respiratory)	40 (66%)	28 (47%)	11 (37%)

OD, oral desensitization; /, and/or; DBPCFC, double-blind placebo-controlled-food challenge.

Table 3. Comparison of active intervention and control groups at baseline

Variable*	Control ($N = 30$)	Active ($N = 30$)	Significance†
Age (months)	25.75 (24–35)	26.5 (26–32.25)	$P = 0.61$
Sex (% males)	63.3	50	$P = 0.29$
Lowest concentration of the positive positive skin prick test (end-point titration with fresh whole cow's milk) (mg/mL)	$10^{-3}\times3$ ($10^{-4}\times3$–$10^{-1}\times3$)	$10^{-3}\times3$ ($10^{-4}\times3$–$10^{-1}\times3$)	$P = 0.83$
Threshold dose (mL)	3.75 (0.5–13.75)	10 (0.5–55)	$P = 0.13$
Specific IgE against cow's milk (kU/L)	24 (28.80–35)	15 (3.35–48.7)	$P = 0.80$
Specific IgE against casein (kU/L)	12.56 (5.89–8.47)	11.4 (3–38)	$P = 0.96$

*Data reported as median and range.

†Mann–Whitney *U*-test.

Table 4. Results after 1 year of follow-up

Variables	Active intervention	Control
Tolerance	27 (90%)	7 (23%)
Fresh whole milk skin test threshold dose (mg/mL)	3 ($10^{-2}\times3$–10×3)	$10^{-2}\times3$ ($10^{-4}\times3$–3)
Specific IgE against cow's milk (kU/L)	7 (0.34–54.20)	24.5 (0.34–101)
Specific IgE against casein (kU/L)	2.61 (0.34–54.10)	19.1 (0.34–101)

Relative risk (RR) (95% CI): 7.7 (2.5–25). Oral desensitization offered a sevenfold greater probability of tolerating milk after 12 months of follow-up than in the absence of such treatment. Number needed to treat (NNT) (95% CI): 1 (1–2).

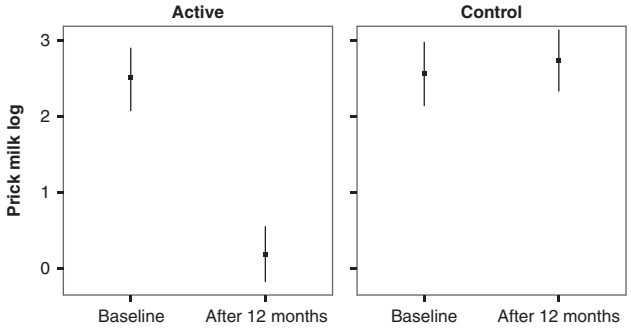

Fig. 2. Evolution of skin sensitivity to fresh whole cow's milk in active intervention group (AG) and control group (CG). End-point skin prick test titration expressed as logarithm of the most dilute concentration yielding a positive papule. Comparison within groups: AG baseline (mean log 2.50, SD log 1.137), after 12 months (mean log 0.962, SD 0.19). Wilcoxon's signed-rank test, $Z=-4.235$, $P<0.0001$. CG baseline (mean log 2.57, SD log 1.13), after 12 months (mean log 2.75, SD log 1.07). Wilcoxon's signed-rank test, $Z=-0.500$; $P=0.617$. Comparison between groups: The difference after 12 months between the active intervention group and control group is significant. Mann–Whitney *U*-test, $P<0.0001$.

cases the parents refused testing (two maintained IgE levels of over 100 kU/L), and another control abandoned the study before testing. A total of seven patients from CG, three with a negative DBPCFC and four who dropped out of the study before final follow-up, were considered tolerant according to an ITT approach (Table 4). A total of 23 children (76.7%) in the control group remained allergic after 12 months of follow-up (Fig. 1).

Mean duration of follow-up in the AG was 14.2 months (range: 12–17 months), while the mean duration of follow-up from the end of oral desensitization was 8.2 months (range: 6–12 months). Mean duration of follow-up in CG was 12.5 months (range: 12–15 months).

The desensitization protocol achieved efficacy with a relative risk (RR) of 7.7, i.e. oral desensitization offered a sevenfold greater probability of tolerating milk after 12 months of follow-up than in the absence of such treatment. In turn, the number needed to treat (NNT) was 1.45

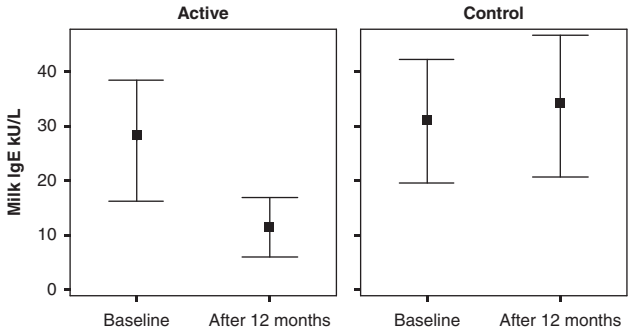

Fig. 3. Evolution of specific IgE against whole cow's milk. AG, active intervention group; CG, control group. Comparison within groups: AG baseline (mean 27.45±SD 28.49 kU/L; median 15 kU/L); after 12 months (mean 11.54±SD 13.84, median 7) Wilcoxon's test: $Z=-3.964$, $P<0.0001$. CG baseline (mean 30.85±SD 30.34 kU/L, median 23.6 kU/L); after 12 months (mean 33.75±SD 34.17 kU/L, median 24.5 kU/L). Wilcoxon's test $Z=-0.360$, $P=0.719$. Comparison between groups: AG and CG at baseline, Mann–Whitney *U*-test: 442, *P*: 0.906; after 12 months, Mann–Whitney *U*-test: 215, $P=0.006$.

(1–2 children), i.e. treatment of a single infant yielded a positive effect (Table 4). Adjusted logistic regression showed no changes of over 10% comparing the crude odds ratio obtained in oral desensitization with the odds ratio obtained when we introduced the following explored variables into the logistical model: threshold doses of the patients in the inclusion DBPCFC milk tests; the baseline levels of specific IgE against cow's milk; and the initial levels of specific IgE against casein.

In AG, a statistically significant increase in the concentration giving rise to a positive skin response was obtained; this effect was not observed in CG (Fig. 2). Significant differences were recorded between groups after 12 months of follow-up (Fig. 2).

Figures 3 and 4 show specific IgE cow's milk and casein serum levels. A decrease in the antibody levels was seen after oral desensitization in AG, but not in CG. Specific IgE milk and casein levels were significantly different in the two groups after 12 months of follow-up (Figs 3 and 4).

In terms of the safety of the oral desensitization protocol, a total of 24 patients (80%) developed some reaction during the treatment period: 14 children developed a moderate reaction (47%); and 10 a mild reaction (33%). Approximately 15% out of the total administered doses (114/738 doses): 17 children presented a reaction with one to four doses; five patients had a reaction with six to 10 doses; One child had a reaction with fourteen doses; and one child had a reaction with fifteen doses. No serious clinical conditions were recorded in any case. The most common manifestations were urticaria-angioedema, followed by cough (Table 2). The symptoms were controlled in each case by oral steroids, antihistamines and/or β_2-agonists and the administration of intramuscular epinephrine was necessary only in two children, once in each case.

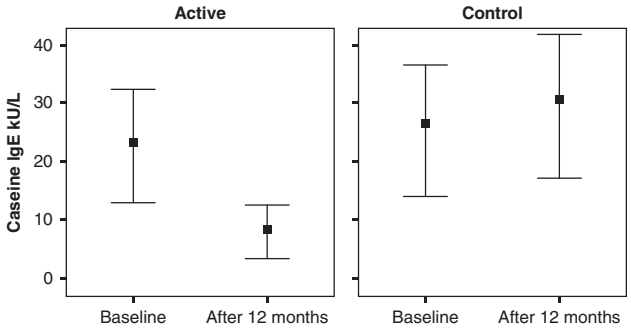

Fig. 4. Course of specific IgE against casein. AG, active intervention group; CG, control group. Comparison within groups: AG baseline (mean 22.58±SD 26.62 kU/L; median 11.4 kU/L); after 12 months (mean 7.89±SD 12.21, median 2.61) Wilcoxon's test: Z −3.77, $P<0.001$. CG baseline (mean 25.32±31.09 kU/L, median 12.56 kU/L); after 12 months (mean 29.47±33.18 kU/L, median 19.1 kU/L). Wilcoxon's test Z −0.360, $P=0.719$. Comparison between groups: AG and CG at baseline, Mann–Whitney U-test: 442, P: 0.906; after 12 months, Mann–Whitney U-test: 215, $P=0.006$.

Discussion

To date, food allergy treatment has almost exclusively been based on food allergen avoidance. Adherence to such exclusion diets becomes increasingly difficult, as the child grows older, particularly when the implicated foods are as common as milk and eggs.

Strict food avoidance difficulties and the risk of reaction have led to research into new therapeutic options for food allergy. A number of treatments are currently being evaluated (subcutaneous immunotherapy [7], administration of anti-IgE [8], specific oral tolerance induction or oral desensitization [9] and sublingual immunotherapy [10]).

In the last decade, a number of studies have reported positive results with oral desensitization to cow's milk. Most of the published series involve patients with severe clinical manifestations and who are over age 5 [11–17].

From this perspective, oral desensitization has been shown to be effective as a second choice treatment strategy, when the exclusion diet measures fail. The present clinical trial was designed to assess an oral desensitization protocol as first-line treatment, i.e. as a therapeutic alternative offering at least the same efficacy as an exclusion diet. This study is the first trial to establish such an objective to evaluate oral desensitization vs. avoidance diet. Two previous studies also used this clinical trial methodology, but they involved older children with severe allergy, and essentially aimed to assess tolerance [14, 20]. The results of this study have been very favourable to oral desensitization, which achieved tolerance in 90% of the treated children vs. 23% in the children who followed the elimination diet. Published studies on oral desensitization point out age (older children) and severity of previous reactions as factors of lower success rates in the oral desensitization procedure [12, 14, 21]. Thus, although our observations are merely preliminary findings, the recorded success in younger children reinforces the benefits of oral desensitization before the age of three.

In our study, we selected 2-year-old patients in order to avoid age bias. Moreover, the design directly compared oral desensitization to CMP avoidance diet. In addition to patient age and the duration of the disease, AG and CG were homogeneous in terms of those variables that might have influenced the results, such as the degree of sensitization (skin reactivity and specific IgE levels) and clinical reactivity (provocation dose). Therefore, the tolerance achieved is attributable to the established oral desensitization protocol and the RR = 7.7 and NNT = 1.45 values obtained favour this therapy as starting treatment in 2-year-old children vs. the food avoidance strategy.

The success of oral desensitization was independent of the degree of baseline skin sensitization and clinical reactivity as assessed by the oral provocation threshold dose before desensitization. However, oral desensitization exerted an effect upon skin and humoral sensitivity, with a significant decrease in skin reactivity and specific IgE levels in the tolerant AG. In comparison, the CG patients maintained the same skin response threshold dosage and specific IgE levels over the entire 12-month follow-up period. This effect, also observed by other authors [12, 17], must be regarded as a consequence of oral desensitization, because it is not seen with the elimination diet.

In our clinical trial, presence or absence of allergy to CMPs was established by double-blind provocation testing. The weak point in our design was the absence of masking for the CG due to the difficulty of maintaining placebo for several weeks at home in the control group. In addition, on completing the oral desensitization protocol, placebo administration would have ended, because the infants with successful oral desensitization would have maintained milk consumption on a continuous basis at home, a situation not possible for the patients given placebo.

Our oral desensitization protocol was found to be reasonably safe. The number of reactions has been high but the majority were considered mild or moderate. The majority of the reactions were presented by only two patients, and only two required epinephrine. The percentage of patients with systemic reactions was lower in oral desensitization than DBPCFC and clinical history (Table 2). Children with anaphylactic shock were excluded, but this allergic manifestation is exceptional in children with CMP allergy in this age group. The only exclusion criteria was a previous clinical history of anaphylactic shock due to milk ingestion. However, 66% of the whole sample reported symptoms (cutaneous/gastrointestinal/respiratory) associated with milk ingestion and 47% of patients

presented this condition as a result of a DBPCFC (Table 2). We therefore included anaphylactic patients. We had no patients with anaphylactic shock, but no patients were excluded due to this criteria; this can be explained by the fact that anaphylactic shock is rare in this age group [22]. More studies are required to focus on identifying risk factors for reactions during the oral desensitization protocol. In our experience, oral desensitization protocols should be performed in Allergy Units with the suitable resources and experienced personnel to manage allergic reactions and all increases of the doses should be administered under supervision at the hospital.

We observed a decrease in skin reactivity and a significant reduction in CMP and casein-specific IgE levels in the active treatment group administered oral desensitization. In comparison, the CG on avoidance diet showed no significant changes after 1 year of follow-up. Over a follow-up period of 18 months, Patriarca et al. [13, 15] also recorded a significant decrease in specific IgE levels and an increase in IgG4 to casein in the patients who successfully completed oral desensitization. Nevertheless, allergen-specific IgG antibody levels are a physiological response of the immune system after exposure to food components and are simply a reflection of the extent of a subject's environmental antigen exposure [23]. Longo et al. [14] observed a significant decrease in cow's milk-specific IgE values measured 6 and 12 months after oral desensitization in 15 out of 30 subjects. It is possible that the cut-off point of 100 kU/L precluded the detection of specific IgE reduction in other subjects in this study.

The fact that our study achieved one of the best percentage tolerances compared with the control group is probably related to the age of the patients, which was far lower than in all of the other studies published to date [12, 14, 21]. This in turn may also account for its increased efficacy.

Although a larger study with more patients is needed, our oral desensitization efficacy and safety results strongly suggest that this treatment could be indicated in allergic children from 2 years of age who have not yet achieved tolerance to CMPs. Oral desensitization could be more effective and possibly also safer in the long term, because tolerance achieved in this period of life could avoid the development of persistent allergy in a significant number of patients [24].

Many children would outgrow their allergy naturally, so a much larger study including many more patients is required in order to weigh up the risks and benefits. We also need markers to identify those patients who are likely to develop tolerance and those in whom the allergy will become persistent.

Clinical relevance

Oral desensitization appears to be efficacious as an alternative to elimination diet in the treatment of 2-year-old children with cow's milk allergy. The oral desensitization side-effect profile appears acceptable but further studies are required to guarantee procedure safety aspects.

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