ORIGINAL ARTICLE

Oral Desensitization in Children With Cow's Milk Allergy

L Zapatero, E Alonso, V Fuentes, MI Martínez

Allergy Department, Hospital Materno Infantil Gregorio Marañón, Madrid, Spain

Abstract

Introduction: Current treatment of food allergies consists of the elimination of the offending food from the diet. Desensitization or tolerance induction can be an alternative for those children who have not achieved tolerance spontaneously. We propose a cow's milk desensitization protocol carried out in an outpatient setting over a 9-10 week period.
Patients and method: Eighteen children older than 4 years with cow's milk protein allergy confirmed by open oral challenge with milk underwent a desensitization protocol beginning with 0.05 mL of cow's milk, reaching 1 mL on the first day, and increasing the dosage weekly until a dose of 200-250 mL of milk taken once a day was tolerated.
Results: By the end of the desensitization protocol, 16 of the 18 patients tolerated 200-250 mL of cow's milk in a single daily dose. The median length of the process was 14 weeks (interquartile range, 11-17 weeks). One patient withdrew due to recurrent symptoms with 2 mL and another reached a tolerance of 40 mL of milk a day. During the program, 11 children (68.75%) presented symptoms that were generally mild but which increased the length of the protocol. At the time of writing, the 16 patients who completed the program continue to tolerate milk, 13 of them for more than a year.
Conclusions: Tolerance of cow's milk was achieved in 16 out of 18 patients who took part in this study. One patient only tolerated 40 mL, which prevents the risk of reactions caused by the inadvertent intake of the food substance; 1 patient is still on a milk-free diet. We believe this cow's milk desensitization protocol to be effective and reasonably safe.

Key words: Cow's milk allergy. Oral food desensitization. Specific oral tolerance induction.

Resumen

Introducción: El tratamiento actual de la alergia a alimentos es la eliminación del alimento responsable de la dieta. La desensibilización o inducción de tolerancia puede ser una alternativa para aquellos niños que no han alcanzado la tolerancia de manera espontánea. Presentamos un protocolo de desensibilización a leche de vaca realizado de forma ambulatoria de 9-10 semanas de duración.
Pacientes y método: Dieciocho niños mayores de 4 años con alergia a proteínas de leche de vaca confirmada por provocación oral, siguieron este protocolo comenzando por 0,05 mL de leche , alcanzando el primer día 1 mL e incrementando las dosis semanalmente hasta tolerar 200-250 mL de leche al día en una toma.
Resultados: Al final del protocolo, 16 de los 18 pacientes alcanzaron la tolerancia de 200-250 mL de leche de vaca en una toma al día, la duración mediana del procedimiento fue de 14 semanas (rango intercuartílico, 11-17 semanas), un paciente abandonó por síntomas repetidos con 2 mL y otro sólo alcanzó la tolerancia de 40 mL de leche al día. Durante el procedimiento 11 niños (68,75%) presentaron síntomas generalmente leves pero que alargaron la duración del protocolo. Los 16 pacientes que finalizaron, continúan tolerando leche, 13 de ellos desde hace mas de un año.
Conclusiones: Se ha alcanzado la tolerancia a leche de vaca en 16 de los 18 pacientes incluidos en este estudio. Un paciente sólo toleró 40 mL, lo que previene el riesgo de reacciones por toma inadvertida del alimento, y un paciente continúa con dieta exenta de leche de vaca. Consideramos este protocolo de desensibilización a leche de vaca efectivo y razonablemente seguro.

Palabras clave: Alergia a leche de vaca. Desensibilización oral con alimentos. Inducción de tolerancia oral específica.

Introduction

Currently the preferred treatment for food allergies is to eliminate the offending food from the diet. In the case of milk, it is extremely difficult to achieve complete dietary elimination, as milk can be masked in a huge and wide-ranging number of processed foods, leading to unwanted reactions that in some cases can be severe.

The natural course of cow's milk protein allergy (CMPA) is the acquisition of tolerance spontaneously through an elimination diet, and 85% of patients overcome CMPA by the time they are 4-5 years old [1-4]. In recent years a number of studies have been published regarding desensitization or tolerance induction to foods, particularly to cow's milk, as an alternative treatment in patients who have not built up tolerance spontaneously [5-12].

Here we present our experience of using a desensitization protocol with milk carried out in an outpatient program over a period of 9-10 weeks, with patients visiting the hospital on a weekly basis to increase the dose.

Patients and Methods

A study was undertaken between December 2004 and April 2006 in 18 children (15 male and 3 female) older than 4 years (mean [SD] age, 5.05 [1.09] years), all diagnosed with CMPA. Informed parental consent was obtained and the study was approved by the ethics committee of Hospital Gregorio Marañón.

Clinical history was recorded and current allergy to cow's milk protein was verified by skin-prick tests (SPT) and analysis of serum specific immunoglobulin (Ig) E (CAP-Phadia, Uppsala, Sweden) using milk and its α-lactalbumin, ß-lactoglobulin, and casein fractions (Bial-Aristegui, Bilbao, Spain), and with open oral challenge. In addition, prick-by-prick tests were carried out using undiluted milk (2.9 g protein per 100 mL) and 1:10, 1:100, and 1:1000 dilutions. In SPT, histamine (10 mg/mL) and saline solution were used as positive and negative controls, respectively. Tests were considered positive when the diameter of the wheal was at least 3 mm greater than the negative control [13]. The open oral challenge with cow's milk began using 1 mL and gradually increasing the dose at 30-minute intervals until symptoms appeared or until a dose of 200 mL, the equivalent of a glass of milk, was reached. Given the refusal by some children to take the food substance, in some cases the milk was disguised using cocoa or the juice of the patient's choice.

Characteristics of the Study Population

All except 1 patient (patient 14) had positive reactions to cow's milk in SPT and had serum specific IgE for whole milk and some of its fractions (Table 1). All patients, including patient 14, tested positive in open oral challenge with milk (Table 2). Patient 14 was included in the study on the basis of her clinical history: she was seen for the first time in our department when 5 months old, having presented vomiting and urticaria on being given adapted formula. At that stage SPT was positive for whole milk and ß-lactoglobulin, and serum specific IgE was 4.48 kU_A/L for milk, 5.19 kU_A/L for ß-lactoglobulin, 0.86 kU_A/L for casein, and negative for α-lactalbumin. During follow-up at 3 years old, the child only tested positive in SPT for ß-lactoglobulin (13 mm), whilst analysis of serum specific IgE

Table 1. Skin Prick Test With Milk and Determination of Serum Specific Immunoglobulin E to Milk and Casein Before and After Desensitization

Patients	SPT With Milk, Wheal Diameter, mm		Serum Specific IgE to Milk, KU_A/L		Serum Specific IgE to Casein, KU_A/L	
	Before Desensitization	After Desensitization	Before Desensitization	After Desensitization	Before Desensitization	After Desensitization
1	9	6	0.51	3.30	0.35	0.45
2	11	Withdrawn	2.93	–	0.86	–
3	6	5	1.39	0.74	1.55	0.72
4	15	18	2.15	2.28	0.95	1.16
5	9	8	0.96	2.96	0.45	0.50
6	7	6	1.27	1.14	0.35	0.35
7	6	6	8.11	7.24	3.99	2.83
8	5	5	0.67	0.49	0.86	0.60
9	7	7	1.04	0.71	0.60	0.47
10	8	3	0.76	0.80	1.08	0.63
11	18	9	12.10	3.97	10.00	0.89
12	13	7	1.19	1.00	1.16	0.35
13	14	7	9.28	4.62	13.10	6.01
14	1	1	0.35	0.35	0.35	0.35
15	6	6	1.62	2.21	0.84	1.31
16	13	7	14.70	6.88	9.47	7.89
17	7	6	3.68	2.78	0.35	1.33
18	9	6	0.48	0.35	0.48	0.35

Abbreviation: IgE, immunoglobulin E.

Table 2. Age of Patients, Symptoms Presented With Open Oral Challenge With Milk, and Treatment Required

Patient	Age, y	Quantity of Milk, mL	Symptoms	Treatment
1	5	85	Urticaria, vomiting, rhinitis	Adrenalin
2	6	1	Cough, pharyngeal itching, urticaria	Anti H1
3	4.5	70	Urticaria	Anti H1
4	4.5	100	Urticaria, vomiting, conjunctivitis	Anti H1, corticosteroids
5	5	15	Rhinitis, pharyngeal itching	–
6	4.5	35	Oral/lingual itching, erythema	–
7	4	40	Urticaria	Anti H1
8	4	30	Facial urticaria	Anti H1
9	4	5	Pharyngeal itching, urticaria	Adrenalin
10	7	10	Rhinitis, conjunctivitis	Anti H1
11	5	50	Rhinitis, conjunctivitis, urticaria	Adrenalin
12	5	5	Pharyngeal itching, facial urticaria	Anti H1
13	5	90	Urticaria	Anti H1
14	4	30	Rhinoconjunctivitis and tightening of the throat	Adrenalin
15	4	7	Urticaria	Anti H1
16	8	10	Urticaria, nausea	Anti H1
17	5	1	Labial edema, facial urticaria	Anti H1
18	6	1	Urticaria	Anti H1

Abbreviation: Anti H1, H1 antihistamines.

for whole milk and all its fractions, including ß-lactoglobulin, was negative. Open oral challenge with milk was positive with 35 mL, which caused urticaria and rhinoconjunctivitis. It was therefore recommended that the patient continue on a milk-free diet. At the 4-year check-up, SPT and analysis of serum specific IgE were negative, but open oral challenge with milk produced quite marked rhinoconjunctival symptoms, with hoarseness, a strange sensation in the body, dysphonia, and difficulty swallowing, requiring treatment with adrenaline, and after which she was included in the desensitization protocol.

Before taking part in the study, 10 (55.5%) of the 18 patients had presented symptoms caused by the accidental or inadvertent intake of milk. Of these, 6 had suffered a single allergy episode, 3 had suffered 2 allergy episodes, and 1 patient had presented symptoms on 3 occasions.

Desensitization Protocol

Tolerance induction was carried out in the outpatient allergy department. Increasing quantities of milk were administered, and the patient remained under observation for at least an hour. The child continued to take the tolerated quantity at home on a daily basis; visits to the hospital were weekly and if tolerance was high, the dose was increased up to a maximum of 200-250 mL of milk taken once a day, the quantity considered tolerable.

Families were given training in the recognition of adverse reactions, the assessment of their seriousness, and their treatment with antihistamines and adrenaline.

For the dosage increase, the protocol described in Table 3 was used. On the first day in the outpatient department, patients took up to 1 mL of milk in fractionated doses (0.05, 0.1, 0.3, and 0.6 mL) at 30-minute intervals. On the second day they took a single dose of 1 mL and then a 2-mL dose 30 minutes later, continuing with this dosage at home on a daily basis throughout the week. Subsequently, they came to the hospital once a week to increase the doses, measured according to tolerance and up to a maximum individual dose of 200-250 mL of milk a day.

At the end of the program, cutaneous tests using milk at the dilutions previously mentioned were repeated, and serum specific IgE for milk and its fractions were determined. The condition of the patients was checked by telephone a month later and if tolerance was found to be good, they were allowed to resume a normal diet with milk drunk freely at this point. After 6 and 12 months, patients returned to the hospital for observation, at which point SPT and serum specific IgE determinations were repeated.

Table 3. Desensitization Protocol

Day	Dose, mL	
	Clinic	Home[a]
1 (Week 1)	0.05, 0.1, 0.3, 0.6	–
2 (Week 1)	1 2	2
9	5	5
16	10	10
23	20	20
30	40	40
37	60	60
44	100	100
51	150	150
58	200	200
65 (Week 10)	250	250

[a] Continued at home until next hospital visit.

Statistical Analysis

Statistical analysis was performed using SPSS version 13.0 (SPSS Inc, Chicago, Illinois, USA). For description of quantitative variables the median and interquartile range (IQR) were used. The means of non-normally distributed variables—SPT results and serum specific IgE, before and after desensitization and at 6-month follow-up—were compared by Wilcoxon signed-rank test. Differences were considered significant when $P < .05$.

Results

In our study, 14 out of the 18 children followed the established protocol, whilst the remaining 4 began by taking higher doses of milk since they had presented symptoms when given large quantities of milk during the open oral challenge test. Table 4 shows the amount of time it took for each patient to achieve tolerance, a period varying from 9 to 32 weeks (median, 14 weeks; IQR,11-17 weeks).

Patient 2 presented pharyngeal pruritus and a tightening of the throat on 3 separate occasions, but as the single-blind open oral challenge test conducted to confirm the reaction proved negative, the patient withdrew from the study.

Patient 6 took no more than a 40-mL dose of milk due to abdominal pain, stinging in the mouth, perioral erythema, and other symptoms that were difficult to evaluate but which prevented increasing the dose. Due to this and the added problem of the anxiety of the mother, the process was halted

Table 4. Symptoms, Treatment, Length of Protocol, and Tolerance Associated With Desensitization to Cow's Milk

Patient	Milk Dosage	Symptoms	Treatment	Length of Protocol	Tolerance, mo
1	100 mL	Vomiting	None	12 weeks	12
2	2 mL on several occasions	Oropharyngeal pruritus and a tightening of the throat	Oral Anti-H1	Dropped out	–
3	100	Perioral exanthema	None	10 weeks	12
4	–	–	–	10 weeks	12
5	5 mL	Perioral erythema	None	16 weeks	12
6	10, 20, 30 mL	Abdominal pain	None	20 weeks	Partial tolerance (40 mL)
7	125 mL	Erythema and facial pruritus	None	16 weeks	12
8	–	–	–	14 weeks	12
9	–	–	–	11 weeks	12
10	–	–	–	14 weeks	12
11	–	–	–	10 weeks	12
12	20, 30 mL	Perioral exanthema	None	9 weeks	12
13	7, 10, 20 mL	Perioral exanthema	None	14 weeks	12
14	50 mL	Rhinoconjunctivitis, vomiting, cough and dysphonia	Anti H1, adrenalin	20 weeks	
15	5, 40, 50 mL	Urticaria and cough	Anti H1, corticosteroids	23 weeks	8
16	2, 3, 4, 5 mL	Oral allergy syndrome, abdominal pain, nausea and urticaria	Anti H1, adrenalin	32 weeks	8
17	10, 15, 30 mL	Pharyngeal pruritus	None	17 weeks	12
18	3 mL	Perioral exanthema	None	13 weeks	8

Abbreviation: Anti H1, H1 antihistamines.

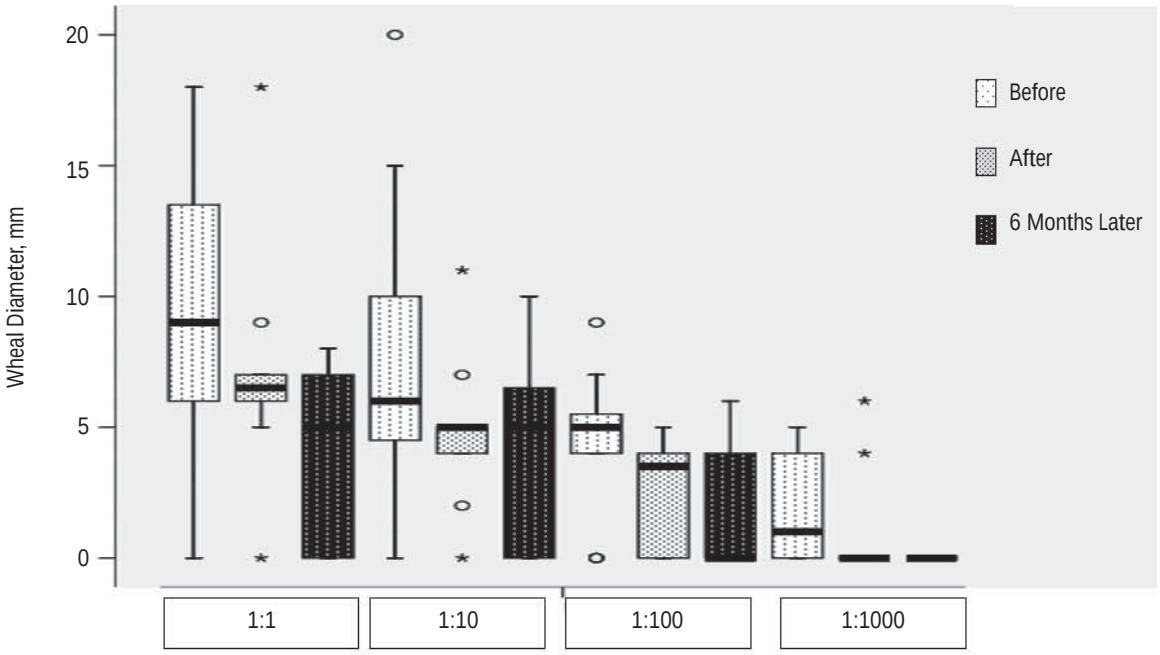

Figure 1. Median wheal size in prick-by-prick tests with whole milk and 1:10, 1:100, and 1:1000 dilutions before and after desensitization and at 6-month follow-up. Whiskers show interquartile range. * and _indicate outliers, extreme values that are not included in the quartiles.

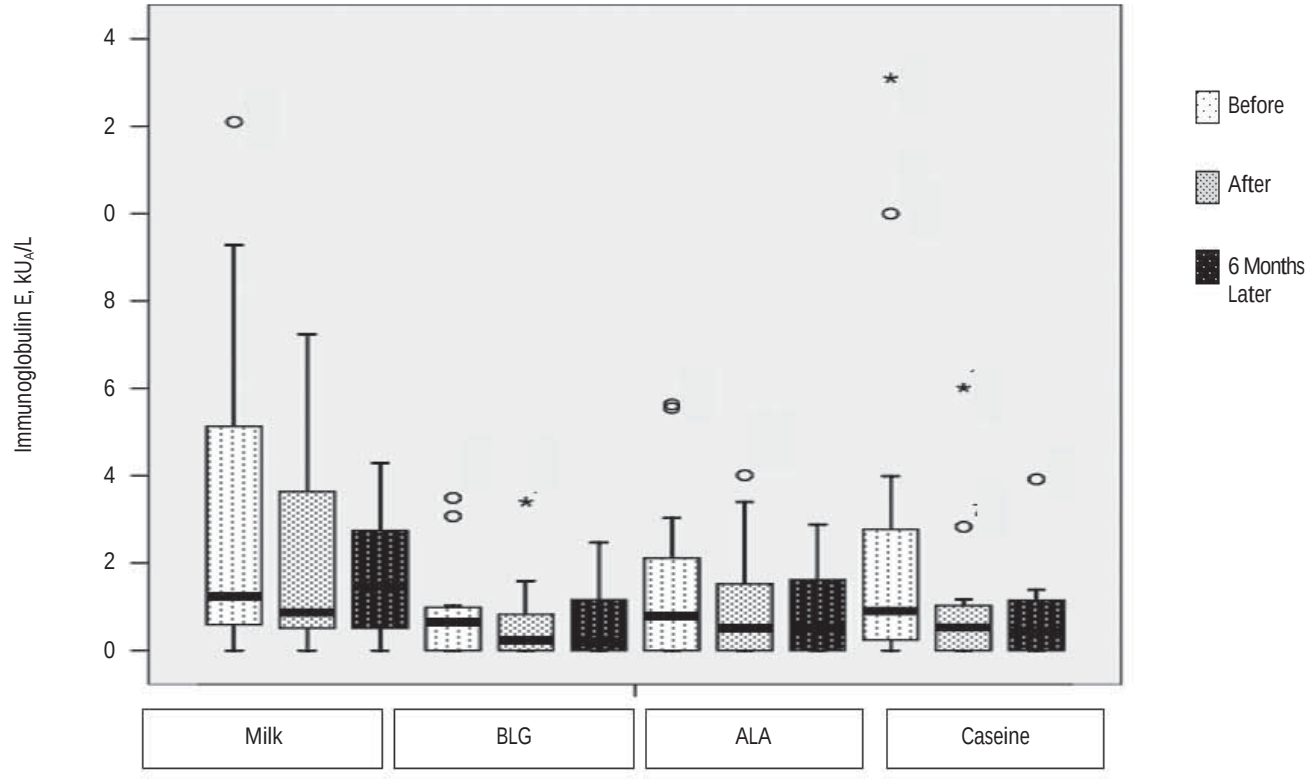

Figure 2. Median value of serum specific immunoglobulin E for milk and its fractions before initiating desensitization, on completing the protocol, and at 6-month follow-up. ALA indicates α-lactalbumin; BLG, ß-lactoglobulin. Whiskers show interquartile range. * and o show outliers, extreme values that are not included in the quartiles.

and the patient asked to continue with just 40 mL of milk a day.

The remaining 16 children attained doses of 200-250 mL of milk taken once a day, and once tolerance of that dose over a period of 1 month was confirmed, they were prescribed a normal diet without restriction of milk consumption.

During the desensitization period, of the 16 patients who completed the program, 11 (68.75%) presented symptoms with 1 or more doses (Table 4). In 8 of the children the symptoms were mild and did not require treatment, although the length of the desensitization process was increased. In 3 cases the symptoms were more significant—urticaria, vomiting, cough, and dysphonia—and required treatment with adrenaline in patients 14 and 16 and oral corticosteroids and antihistamines in patient 15. In 3 patients, the time needed to achieve tolerance was considerably longer: 20 weeks in patient 14, 23 weeks in patient 15, and 32 weeks in patient 16 (Table 4).

Figure 1 shows the median and IQR for SPT with whole milk and 1:10, 1:100, and 1:1000 dilutions prior to desensitization, immediately after completion of the protocol, and at 6-month follow-up. There was a clear reduction in wheal diameter at the end of the desensitization protocol that was statistically significant for 1:1 ($P = .028$), 1:10 ($P = .032$), and 1:100 ($P = .021$) dilutions, and for all dilutions at 6-month follow-up: 1:1 ($P < .001$), 1:10 ($P = .013$), 1:100 ($P = .008$), and 1:1000 ($P = .016$).

Figure 2 shows the median and IQR for the levels of serum specific IgE for milk and its fractions before and after desensitization, and at 6-month follow-up. A decrease in all the values was observed, although the difference was only statistically significant for casein at the end of the protocol ($P = .012$) and at 6-month follow-up ($P = .019$).

Of the 16 patients who completed the desensitization protocol, all 16 continue to tolerate a normal diet without restriction of milk consumption, 13 of them after a year and 3 for the past 8 months (Table 4).

Discussion

Currently, when a diagnosis of CMPA is established the only treatment is an elimination diet and therapeutic measures in the case of accidental ingestion of the food substance. Nevertheless, milk can be inadvertently ingested via processed foods, and it is therefore essential that parents and children take special care when reading the labels. Despite precautionary measures, it is estimated that as many as a third of the children who observe a milk-free diet present symptoms, which are sometimes severe, caused by accidental intake [14]. This latent danger, which is impossible to control completely, leads to a feeling of insecurity in patients and their caregivers, thus significantly worsening their quality of life [15]. In addition, there is an increased likelihood that CMPA will turn into a persistent allergy from the age of 4-5 years [2,3]. Consequently, efforts have been made to identify alternatives to the elimination diet, including desensitization or tolerance induction.

Patriarca and colleagues [11] published a desensitization protocol that began with 1 drop of milk and culminated in 120 mL over a period of 136 days; 59 patients with varying food allergies, of which 16 were children with CMPA, took part in that study. Of those 16 children, 13 (76.9%) completed the desensitization in 3-12 months, while 3 had to withdraw from the program due to severe adverse effects.

Bauer and colleagues [7] reported rapid oral desensitization carried out in a 12-year-old girl admitted to hospital with urticaria and angioedema caused by cow's milk. They began the process with 0.01 mL of milk and, by doubling the dose, reached 200 mL on the fifth day. The authors recommended that this protocol only be performed under strict medical supervision.

Meglio et al [12] published a desensitization protocol that was successful in 15 out of 21 children (71.4%) with CMPA. Their method began with 1 drop of a 1:25 dilution of milk increasing to 200 mL on day 180 (6 months). Three patients withdrew from the protocol due to minimal symptoms. Those authors placed particular emphasis on 3 children who achieved partial tolerance at 40-80 mL a day, since under those conditions the risk of severe reactions following accidental ingestion is dramatically reduced.

In our study, 16 of the 18 participating patients (89%) achieved a tolerance of 200-250 mL of milk a day. One patient abandoned the study on presenting repeated symptoms with 2 mL of milk. Another only achieved a partial tolerance of 40 mL taken once a day, which protected him from reactions to small quantities taken accidentally. These 2 patients took part in another desensitization protocol conducted a few months later and are currently on a normal diet without restriction of cow's milk intake.

In our study, 11 of the patients (68.75%) presented symptoms with 1 or more doses. Symptoms were generally mild, such as oral pruritus or perioral exanthema that went away either spontaneously or with oral antihistamines. Three of the patients (patients 14, 15, and 16) presented moderate symptoms (urticaria, abdominal pain, cough, vomiting, and dysphonia) that were cured in 1 case with antihistamines and corticosteroids and required adrenaline in the other 2 patients. Generally, symptoms occurred in the hospital when the dose was increased, and therefore it would be ill-advised to increase doses without medical supervision.

Patriarca and colleagues [11] used cromoglycate prior to the milk dose in order to minimize the side-effects. Throughout their program, Meglio and colleagues [12] administered treatment with cetirizine, which patients stopped a week after reaching the final dose. Patriarca and colleagues reported symptoms during the program in 51.5% of patients using cromoglycate and Meglio and colleagues observed symptoms in 61% with cetirizine. It is possible that the use of antihistamines during the program might eliminate mild symptoms such as oral pruritus or perioral eruptions that in some cases meant that the dose had to be repeated or increased at a slower pace.

The protocol was initially due to last 9-10 weeks but ended up lasting an average of 14 weeks, ranging from 9 to 32 depending on the patient. In Table 4 we can see that the patients who required a longer period to reach the final dose were those who also presented more severe symptoms during the program (patients 14, 15, and 16), since it was necessary

not only to reduce the doses but also to repeat some and proceed more slowly. In patients with minor symptoms it was also necessary to repeat certain doses. Likewise, when concomitant disease arose (asthma attack, renewed worsening of atopic dermatitis, respiratory infection, etc) the quantity of milk was not increased.

In SPT and analysis of serum specific IgE we did not find any common feature in these patients that could have allowed us to predict difficulty in following the program (Table 1). Prick-by-prick tests were negative in patient 14, 6 mm in patient 15, and 13 mm in patient 16, while serum specific IgE was negative in patient 14, 1.62 kU_A/L for whole milk in patient 15, and 14.7 kUa/L in patient 16; similar results were obtained with α-lactalbumin, ß-lactoglobulin, and casein fractions in both SPT and analysis of serum specific IgE. Despite the fact that she had negative results for both serum specific IgE and SPT, patient 14 was included in the study due to her clinical history and because positive provocation led us to believe that specific IgE was undetectable at that moment with the methods used.

In this study, we did not carry out double-blind, placebo-controlled food challenge (DBPCFC), which is the method recommended in research studies. Instead, we used the standard method practiced in practical clinical pediatrics, that of open oral challenge [16]. Since various studies using DBPCFC methodology have demonstrated the effectiveness of desensitization with milk [11,12] and other food substances, our use of open oral challenge does not undermine the validity of a therapeutic alternative which can be offered to patients who have not achieved tolerance to milk spontaneously and which can conclusively change their prognosis and hence their quality of life [17,18].

Of the 16 patients who successfully reached the final dose of 200-250 mL of milk, 13 continued to tolerate cow's milk after 12 months of follow-up and the other 3 were still tolerant after 8 months. Currently, all are following a normal diet for their age group with respect to this food substance, a common feature in our diet.

We identified a reduction in levels of specific IgE for milk and its fractions and a more notable decrease in the results of prick-by-prick tests with milk dilutions. Consistent with the findings of other researchers [11], the decrease was slow and did not allow prediction of course.

We do not know for what length of time milk must be taken on a daily basis for the tolerance to be maintained. Rolinck-Werninghaus et al [19] published an article recently in which they reported how 3 patients who had undergone tolerance induction—for milk in 1 case and for egg in 2 others—had their intake of the food substance stopped for 2 weeks. When intake was resumed, they began to present symptoms again.

We believe that research needs to be done to identify biomarkers capable of indicating the difference, if there is one, between spontaneous and desensitization-induced tolerance. This would allow us to recognize when tolerance is permanent.

We consider that desensitization or tolerance induction to cow's milk is an effective and reasonably safe treatment. We believe it feasible to offer this as a real therapeutic alternative to children older than 4-5 years in whom there is a high likelihood that CMPA will remain a persistent problem. Our protocol was not considered unpleasant by the patients (children and parents). This program should be administered by professionals who are highly trained in the recognition and early treatment of allergic reactions to foods and always in an environment adequately equipped to deal with any adverse reaction. It remains to be clarified whether the acquired tolerance is transitory or whether at any point it becomes definitive.

Acknowledgments

The authors would like to thank Teresa Pérez, Teresa Fernández, and Patricia González for providing excellent nursing support.

References

1. Host A. Clinical course of cow's milk protein allergy and intolerance. Pediatr Allergy Immunol. 1998;9(11):48-52.
2. Host A, Halken S, Jacobsen HP, Estmann A, Mortensen S, Mygil S. The natural course of cow's milk protein allergy / intolerance. J. Allergy Clin Immunol. 1997;99;1:S490
3. Bishop JM, Hill DJ, Hosking CS Natural history of cow milk allergy: Clinical outcome. The Journal of Pediatrics. 1990;116:862-7.
4. Alvarado MI, Alonso E, Gª Álvarez M, Ibáñez MD Laso MT. Persistencia de sensibilización a proteínas de leche de vaca: estudio clínico. Allergol et Immunopathol. 2000;28(3):189.
5. Patriarca G, Romano A, Venuti A. Schavino D. Di Renzo V, Nucera. Oral specific hyposensitization in the manegement of patients allergic to food. Allergol Immunonopathol. 1984;12:275-81.
6. Poisson A, Thomas G, Jean –Landis N, Giaufre E. Accoutumance rapide par voie orale au lait de vache dans un cas d´allergie alimentaire sévère chez l´enfant. Rev Fr, Allergol. 1987;27(1):31-2.
7. Bauer A. Ekanayake S, Wingger-Alberti, Eisner P. Oral rush desensitization to milk. Allergy.1999;54:894-5.
8. Martorell A, Pérez C, Cerdá JC, Ferriols E, Vila R Álvarez V. Inducción de tolerancia clínica en Alérgicos a leche de vaca. Allergol. et Inmunopathol. 2002;30(3):183.
9. Zapatero L, Alonso E, Molero MI. Desensibilización oral a leche en niños. Allergol et Immunopathol. 2005;33(1):59-60.
10. Boissieu D, Dupont D. Sublingual immunotherapy for cow´s milk protein allergy: a preliminary report. Allergy. 2006;61:1238-9.
11. Patriarca G, Nucera E, Roncallo C, Pollastrini E, Bartolozzi F, De Paquale. Oral desensitizing treatment in food allergy: clinical and immunological results. Aliment. Pharmacol Ther. 2003;17:458-65.
12. Meglio P, Bartone E, Plantamura M, Arabito E, Giampietro PG. A protocol for oral desensitization in children with IgE mediated cow´s milk allergy. Allergy. 2004;59:980-7.
13. European Academy of Allergology and Clinical Immunology. Position Paper: allergen standardization and skin test. Allergy. 1993;48:48-82.
14. Alonso E, Fernández L, Somoza ML. Alergia a leche y huevo en niños. Alergol Inmunol Clin. 2001;6:96-110.
15. Sicherer SH, Noone SA, Muñoz-Furlong A. The impact of

childhood food allergy on quality of life. Ann Allergy Asthma Immunol. 2001;87:461-4.
16. Comité de Reacciones Adversas a alimentos, Ibáñez MD, Alonso E, Blanco C, Cisteró AM, Cuesta J, Fernández-Rivas M, Florido JF, Gª Figueroa B, Laffond E, Martín F, Nieto A, Rico MA, Rodríguez J. Metodología diagnóstica en la alergia a alimentos. Alergol Inmunol Clin. 1999;14(2):50-62.
17. Longo G, Berti I, Barb E. To throw the baby out with the bathwater: double blinding for specific oral tolerance induction. Allergy. 2007;62:82.
18. Niggeman B, Staden U, Rolinck Werning-Haus C, Beyer K. Specific oral tolerance induction in food allergy. Allergy. 2006;61:808–811.
19. Rolinck-Werninghaus C, Staden U, Mehl A, Hamelmann E, Beyer K, Niggemann B. Specific oral tolerance induction with food in children: transient or persistent effect on food allergy? Allergy. 2005;60:1320-2.

Manuscript received February 28, 2007; accepted for publication December 12, 2007.

Lydia Zapatero Remón

Avda. Dr. García Tapia, 157 E-4º A
28030 Madrid, Spain
E-mail: lzapatero.hgugm@salud.madrid.org