

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

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SUMMARY:

■ **Background:** Food allergy is treated by avoidance diets in order to prevent anaphylactic reactions and to cure chronic associated symptoms. However, the natural history is left unchanged.

■ **Objective:** To search for a beneficial effect of an oral desensitization protocol to allergenic foods in IgE-dependent milk or egg allergies in children

■ **Methods:** 60 children with documented cow's milk allergy (13 months-6.5 years), and 90 children with egg allergy (12 months-8 years), were consecutively included after 6-12 months of avoidance diet, if a SBPCFC to 60 ml milk (60 ml) or to 965 mg of raw egg white was negative. They were randomized for uninterrupted avoidance or oral desensitization (group A or OD). Six months later, a new SBPCFC was performed with, up to 200 ml of milk or 7g of raw egg white. Prick tests and specific IgE levels were carried out simultaneously.

■ **Results:** Data were obtained for 57 children with CMA (30 A and 27 OD), and 84 children with EA (35 A and 49 OD). The two groups (AD or OD group) were similar with regard to means of ages, the size of PT wheals and the level of IgEs at baseline.

■ **Milk allergy:** A SBPCFC to milk was positive in 11.1% of those following OD vs. 40% after A ($p < .025$). The size of PT decreased after OD and increased after A (-3.4 mm vs. +0.84 mm; $p < .002$).

■ **Egg allergy:** The SBPCFC to egg was positive in 30.6% after OD vs. 48.6% after A ($p < .1$). After 6 months, in the OD group, the mean size of the PT and the level of specific IgE were significantly reduced compared to the A group. In the A group, the threshold of reactivity was often lower, or more serious symptoms were observed.

■ **Conclusion:** Oral desensitization helps the egg and milk allergic children to overcome their allergies. Since the avoidance of these foods is likely to increase sensitization as well as to lower the threshold of reactivity, an active treatment is required. Further attempts to standardize the procedures of oral desensitization are expected.

Key-words: Milk allergy - Egg allergy - Oral desensitization.

INTRODUCTION

The prevalence of food allergy in children is estimated to be between 6-8% (1), with 1.9-3.2% representing those with milk allergy (2-5), and 1.6% with egg allergy (6). Currently, the management is only avoidance. The duration of avoidance diets is not based on precise data. The natural evolution of food allergies in children depends to a certain extent on the allergen (7). Bock observed recovery from food allergy in 19% of children under 3 years of age and in 44% of those over 3 years (8). Boyano estimated recovery from food allergy in about 30% under 3 years of age, 40% under 6 years and 50% under 9 years (9).

Recovery from cow milk allergy (CMA) is observed in 56% of children at the age of one year, in 77% at 2 years, 87% at 3 years, 92% at 5 and 10 years, and 97% at 15 years (10). The study of Bishop et al. reported recovery in 28% of children aged 2 years, in 56% at 4 years and in 78% at 6 years (11). The number of spontaneous recoveries is lower in IgE-mediated allergies and poor (22% at 2 years) when CMA is included in a multiple food allergy (10, 12). Spontaneous recovery from EA occurs later, and persists in 34% of children at 5 years (13). After 2^{1/2} years of an avoidance diet, only 44% of children are cured as evaluated by OC (14, 15).

Although strict avoidance prevents severe anaphylaxis and helps to minimize associated chronic diseases (atopic dermatitis, asthma, etc.), it cannot be considered as a real treatment since severe anaphylactic reactions have been described after a long avoidance diet (16). Other therapeutic solutions have been attempted, such as treatment by anti IgE (17), or oral

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desensitization (OD) (18-23). Successful results of OD have been reported in milk or egg allergies but studies have not been randomized.

This study was carried out in 60 children with CMA and 90 with EA. The primary aim was to analyze the rate of recovery induced by oral desensitization, compared to the natural evolution after avoidance, over a 6 month period. The secondary aim was to assess immunological modifications of prick tests and of specific IgEs.

METHODS

Population investigated

60 children (21 females, 39 males) with CMA, aged between 13 months and 6.5 years (mean: 2.2 ± 1 years). 54 had atopic dermatitis, 7 had urticaria and angioedema, 9 had asthma and 8 had gastrointestinal symptoms (table1).

90 children were allergic to egg (32 females, 58 males), aged between 12 months and 8 years (mean: 3.5 ± 1.7 yrs): 79 had atopic dermatitis 14 had urticaria and angioedema, 33 had asthma and 4 had gastrointestinal symptoms (table 2).

Food allergy had been established on the basis of sensitization (positive prick test and/or the presence of specific IgE, and allergy confirmed by either positive labial or oral food challenge, or complete recovery from symptoms after 3 weeks of avoidance of CM in

infants (DBPCFC not performed in infancy) (24-25). In 15 cases, the diagnosis of non IgE-mediated milk allergy (negative prick tests and RAST), was established only by positive oral food challenge and/or recovery after 3 weeks of an eviction diet.

■ **Design of the study:** Egg or milk allergic children were examined for the follow-up, 6 months to one year after diagnosis and continuous avoidance. The following tests were performed: prick tests with O Lac® milk or REW, assay of specific IgE for both foods (IgE1) and a placebo-controlled food challenge. Subjects were selected on the basis of non-reactivity to 60 ml of milk or to 965 mg of REW, in order to turn down most sensitive patients. Patients were randomized with a random numbers table, odd numbers being distributed in the A group, continuing avoidance, and even numbers in the OD group (oral desensitization).

The children were examined again after 6 months and underwent the same tests (prick test, specific IgE and SBPCFC). Recovery was confirmed if the child regularly ate the food or if the challenge was negative with 200 ml of milk or 7g of REW, leading to the routine ingestion of the food.

■ **Skin prick-tests:** They were carried out with natural foods: O Lac® milk, without lactose (Mead Johnson laboratories) and raw egg white (26). 9% codeine phosphate and glycol-saline were used as positive and negative controls. Wheal diameters > 50% of the size of the positive control were considered positive.

■ **Food-specific IgEs:** They were measured with cap system FEIA (Pharmacia Sweden).

	AD	Urticaria and/or AE	Asthma	GI signs: Vo, diarrhea, abdominal pain	FtT
Group A n = 32	87.5% (28)	12.5% (4)	15.5% (5)	6% (2)	0% (0)
Group OD n = 28	96% (26)	11% (3)	15% (4)	22% (6)	7% (2)

Table 1: Clinical signs of cow's milk allergy presented by the 60 children included in the A and OD groups.

AD: atopic dermatitis; AE: angioedema; Vo: vomiting; FtT: failure to thrive; GI: gastro-intestinal.

	AD	Urticaria and/or AE	Asthma	GI signs: Vo, diarrhea, abdominal pain
Group A n = 39	85% (33)	18% (7)	33% (13)	5% (2)
Group OD n = 51	90% (46)	14% (7)	39% (20)	4% (2 with abdominal pain)

Table 2: Clinical signs of egg allergy presented by the 90 children included in the A and OD groups.

AD: atopic dermatitis; AE: angioedema; GI signs: gastro-intestinal signs; U: urticaria; Vo: vomiting.

■ **SBPCFC:** SBPCFC were carried out during a 24-48 hour hospitalization period after written informed consent from the parents. Medical monitoring included pulse, blood pressure, lung auscultation and peak flow rate (PFR) in older children and skin and oral cavity inspection (27).

A lactose-free milk formula was used (O Lac® milk, Mead Johnson laboratories). The vehicle was an amino acid-based formula (Neocate®, SHS laboratories). The milk was administered in incremental doses every 20 minutes as follows:

- Day ₁: 0.1 ml, 0.2 ml, 0.5 ml, 1.5 ml and 4.5 ml (cumulative dose (CD): 6.8 ml).
 - Day ₂: 5 ml, 15 ml and 40 ml (CD: 60 ml).
- Raw egg white (REW) was administered in stewed apples (28-29). The doses increased every 20 minutes as follows:

- Day₁: 5 mg, 10 mg, 50 mg, 200 mg and 700 mg (CD: 965 mg).
- Day₂: 500, 1500 and 5000 mg (CD: 7 g).

■ **Oral desensitization protocol:** The parents of children randomized for OD received information concerning the protocol to be followed at home for several weeks. The children randomized for avoidance maintained the previous diet.

OD protocol using whole pasteurized milk:

- First week: Day₁: 1 ml, Day₂: 2ml, Day₃: 5 ml, Day₄: 10 ml, Day₅₋₇: 20 ml.
- Second week: 50 ml/day.
- Third week: 100 ml/day.
- Fourth week: 100 ml/day and introduction of cream desserts, yoghurts or cream cheese.
- Fifth and sixth week: 250 ml/day and dairy products.
- Seventh week and thereafter: routine amounts, not quantified.

OD protocol using hard-boiled eggs:

- First week: 1 g of egg yolk once a day, every day.
- Second week: 1 g of yolk and 1 g of EW once a day, every day.
- Third week: 2 g of yolk and 2 g of EW once a day, every other day.
- Fourth week: 4 g of yolk and 4 g of EW once a day, every other day.
- Second month: introduction of biscuits and crackers, etc.
- Third month: introduction of flans, cream desserts.

The following foods were persistently contra-indicated: meringues, vacherins, chocolate mousse, since they contain insufficiently cooked egg white.

Statistical analysis of results: The following parameters were studied: age, mean diameter of PT wheals, specific IgE levels. A Student's test was used to compare means of initial PT, specific IgE and the same parameters 6 months later, in the two groups.

The Chi squared test was used to compare the failure and recovery rates in the two groups; p was considered significant if $\leq .05$.

RESULTS

Milk allergy

Three children were lost to follow-up: 2/32 in the A group and 1/28 in the OD group. The analysis was carried out on 57 children, respectively 30 A and 27 OD. Children in both groups presented atopic dermatitis, urticaria and/or angioedema, vomiting, diarrhoea,

abdominal pain, asthma and failure to thrive. Some children in each group presented several symptoms simultaneously (table 1).

Groups A and OD were similar for respectively, mean age: 2 years [1-4] and 2.4 years [1-7]; standard deviation (SD): 0.8 vs. 1.2, mean PT to milk: 2 mm [0-7] and 2.8 mm [0-10]; SD: 2.0 vs. 2.4 and specific IgE levels 3.4 kU/l [0.34-24.4] and 3.42 kU/l [0.34-21]; SD: 5.5 vs. 5.5 at baseline (Student's test $p > .1$) (figure 1).

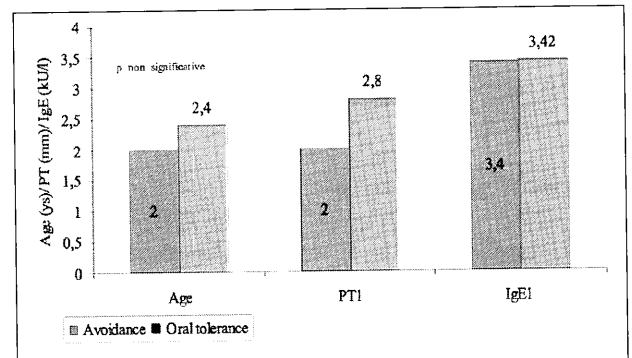


Figure 1: Comparison of parameters (mean age, mean size of prick test wheals and IgE levels) of children allergic to milk on avoidance diet (A) and in oral desensitization (OD) group.

After 6 months, 12 children in group A, i.e. 40%, failed to pass the oral challenge. In 7 children the cumulative reactive dose was lesser than that used in the first SBPCFC: the lowest threshold dose was 2 ml. There were more severe symptoms than during the first challenge, particularly in 2 cases with onset of urticaria, angioedema and vomiting at 25 ml, and malaise and lethargy with 50 ml. In the OD group, three (11.1%) discontinued milk during the OD between day 7 and day 20, due to clinical reactions (table 3). Two of these had a positive oral challenge, confirming the diagnosis of persistent milk allergy. The third was not re-challenged. After 6 months, 24/27 (88.9%) regularly drank milk without symptoms. SBPCFC was negative to 200 ml in all these cases.

The results depend on the type of CMA. Children with gastrointestinal symptoms often recovered spontaneously (5/8 in the A group, 6/7 in the OD group). Conversely, in IgE mediated allergy, only 12/22 in the A group but 18/20 in the OD group recovered spontaneously ($p < .025$) (figure 2). There was no relation between outcome (recovery or persistent allergy) and the status of associated food allergies (data not shown).

After 6 months, the mean of PT wheal size was higher in the A group than in the OD group (2.7 vs. 1.4 mm; $p < .05$) (figure 3). The gap between the first and the second PT increased in the A group (+0.84 mm) and

decreased in the OD group (-3.4 mm) ($p<.002$). There was a significant decrease in the PT wheal before and after the OD protocol (2.8 vs. 1.4 mm; $p<.025$) (figure 3).

The evolution of sensitization was compared in each group depending on recovery or persistence of the allergy.

Within the A group, the size of the PT wheal increased and the level of specific IgE decreased in both sub-groups (ns). Children with persistent CMA had larger PT to milk than cured children (2.8 vs. 1.5 mm; $p<.05$) (figure 4).

Within the OD group, three children had a persistent gastrointestinal allergy. In the "recovery" subgroup, the mean size of the PT decreased over 6 months from 2.8 to 1.2 mm ($p<.005$), and remained unchanged in the "failure" group (2.8 then 2.7 mm) (fig. 4). Specific IgEs decreased in both groups. However, the decrease in IgE was greater in the "recovery" subgroup: 3.07 vs. 1.6 kU/l ($p<.1$) and 8.21 vs. 6.7 kU/l in the failure subgroup (p ns).

Group	Failures (N°)	CTD (ml)	AD	U	AE	GI signs	Lethargy
A n = 30	1	2		X			
	2	25		X	X	vomiting	
	3	25		X			
	4	50					X
	5	1 teaspoon of yoghurt			X		
	6	5	X				
	7	50	X				
	8	63	X				
	9	150	X				
	10	200	X				
	11	200	X				
	12	60	X			diarrhea, abdominal pain*	
OD n = 27	1	20				refusal, abdominal pain, FtT*	
	2	50				Vo, diarrhea*	
	3	100				diarrhea*	

Table 3: Clinical signs and threshold doses during the 2nd oral food challenge to milk at 6 months, or at home during the oral desensitization in A and OD groups (tolerated 60 ml at the first oral challenge).
*: symptoms recurred during challenge at home.
D: atopic dermatitis; AE: Angioedema; CTD: cumulative threshold dose; FtT: failure to thrive.
GI: gastro-intestinal; U: urticaria; Vo: vomiting.

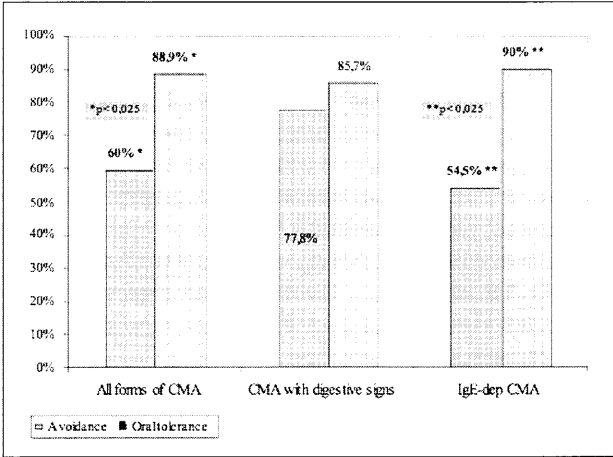


Figure 2: Comparison of the percentage of milk allergy recovery between the A and OD groups.

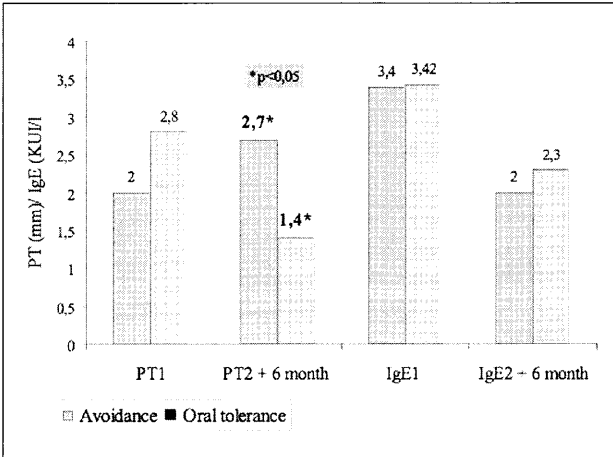


Figure 3: Comparison of the prick-tests and milk specific IgE evolution between the A and OD groups.

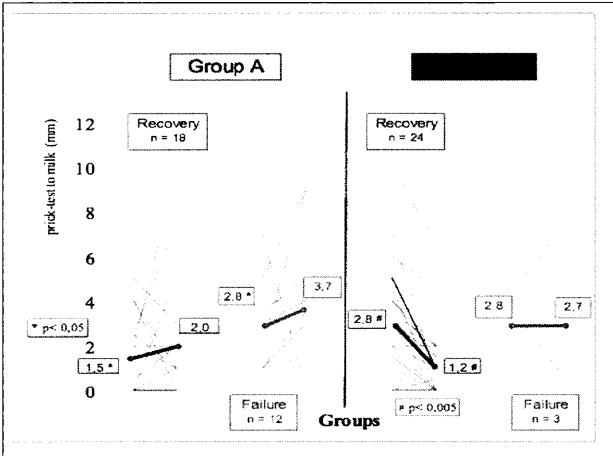


Figure 4: Comparison of the evolution of prick tests to milk over 6 months in the group on avoidance diet (A) and the group following an oral desensitization to milk (OD).

ALLERGY TO EGG

Four out of 39 children in the A group and 2 out of 51 in the OD group were lost to follow-up. In both groups clinical symptoms were: atopic dermatitis, urticaria and/or angioedema, various gastrointestinal signs (vomiting, diarrhoeas, and abdominal pain (table 3). The A (n = 35) and OD (n = 49) groups were similar with respect to age (mean: 3.6 vs. 3.5 years; SD: 1.7 vs. 1.8), prick test to raw egg white (mean: 7.1 vs. 7.2 mm; SD: 3.5 vs. 4.3) and level of specific IgEs (mean: 4.98 vs. 3.8 kU/l; SD: 12.8 vs. 8.0) at baseline respectively (figure 5).

Six months later, the mean size of PT and the mean level of specific IgE were significantly different between group OD and group A: respectively PT (4.6 vs. 7.04 mm; SD: 4.0 vs. 4.6; $p < .05$) (2.0 vs. 3.56 kU/l; SD: 4.3 vs. 11.11; $p < .01$).

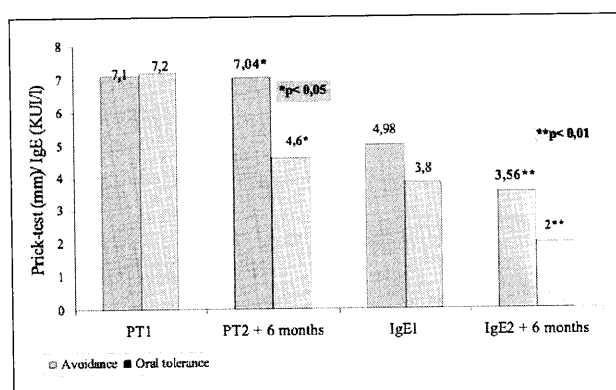


Figure 5: Comparison of the parameters: means of the prick tests and specific IgE to egg, between the group on egg avoidance diet and the oral desensitization group, at the beginning of the study and six months later.

In the A group, 17/35 (48.6%) had a persistent food allergy 6 months later. For 9 children, the cumulative reactive dose was lower than that of the first SBPCFC. Urticaria was noted at 110 mg and 265 mg in children previously presenting only with eczema (table 4). In two cases, a reaction occurred after contact with egg and the labial challenge was graded 3 and 4.

In the OD group, 15 failures out of 49, i.e. 30.6% ($p < .1$), were reported. In some cases, symptoms appeared at home during the first week (1 g of cooked EW) and the fourth week (4 g) of the OD. One child, despite the fact that he had presented with facial angioedema after eating half a hard boiled egg during the OD protocol, seemed to be improved, since before the protocol, he could only tolerate traces of cooked egg, and four months later he presented urticaria only with 640 mg of raw egg white. Another, who tolerated only traces, suffered abdominal pain after ingestion of 110 mg REW during the second oral challenge. A recovery

was obtained in 34 cases (69.4%) (vs 51.4% in the A group). After six months of desensitization, there was a marked decrease in the size of PT wheals (7.2 then 4.6 mm; SD: 4.3 vs. 4.0; $p < .05$) and specific IgE decreased from 3.8 down to 2 kU/l (SD: 8.0 vs. 4.3 $p < .01$) (figure 5). Conversely, in the A group, the mean level of IgE slightly decreased (4.98 vs. 3.56 kU/l; SD: 12.8 vs. 11.1 not significant), and the PT size remained identical (7.1 vs. 7.0 mm; SD: 3.5 vs. 4.6).

Group	Failures (N°)	CTD (ml)	AD	U	AE	GI signs	Other
A n = 35	1	265				diarrhea	asthma
	2	265	x				
	3	110	X				asthma
	4	265		X			
	5	65 *				**abdo pain, diarrhea	otalgia, *purpura in auditory canal
		7000 **					
	6	610	X	X			
	7	610	X				asthma
	8	965		X		Vo	
	9	965	X				
	10	965	X				
	11	1500	X				
	12	6500	X		X		
	13	7110	X				
	14	7110			X	Vo	lethargy
	15	7110				X	
	16	TPL grade IV					
	17	TPL grade III					
OD N = 49	1	110				abdo pain, diarrhea	
	2	610			X		
	3	965			X		
	4	2110	X		X	X	
	5	7110		X			
	6	7110	X			abdo pain	
	7	7110		X		abdo pain	
	8	1000 CEW	X°				
	9	4000 CEW		X°			asthma
	10	4000 CEW					asthma
	11	4000 CEW	X°				rhinitis
	12	4000 CEW	X°				
	13	4000 CEW	X°				
	14	4000 CEW	X°				
	15	8000 CEW	X°				

Table 4: Clinical signs and threshold doses during the 2nd oral food challenge to egg at 6 months or at home during the oral desensitization in groups A and OD. (tolerated 965 mg at the first oral challenge).

AE: Angioedema; CEW: cooked egg white; CTD: cumulative threshold dose; dia: diarrhoea; abdo. pain: abdominal pain; Vo: vomiting.

°: signs occurring during the oral tolerance protocol at home.

Within the A group, a comparison of failures and recoveries showed that the initial mean of PT size to egg was lower in the subgroup that recovered (6 mm vs. 8.3 mm; $p < .05$). Initial mean specific IgE levels were also lower (0.9 vs. 10.6 kU/l; $p < .05$).

Within the OD group, in the subgroup that recovered, the initial mean of PT size to egg was smaller (6.4 mm vs. 8.9 mm; $p < .05$) (figure 6). This difference remained significant after six months (2.3 vs. 6.8 mm; $p < 0.05$). Specific IgE levels were lower (ns).

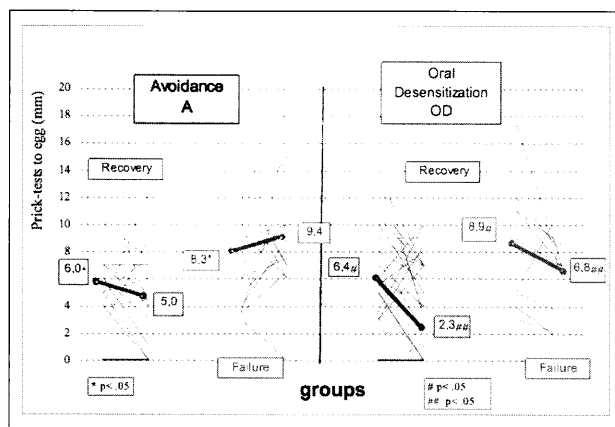


Figure 6: Comparison of the evolution of prick tests to raw egg over 6 months in the group on egg avoidance diet (A) and the group following oral desensitization (OD).

DISCUSSION

This study on a large number of milk and egg allergic children seeks to demonstrate the beneficial effect of oral desensitization. The presence of specific IgEs and positive skin prick tests do not contra-indicate progressive reintroduction (9-10). Oral desensitization was proposed on the basis of no reactivity with 60 ml of milk, or 965 mg of REW. The safety of a progressive reintroduction was based on our personal experience that children not reacting to these doses do not experience severe anaphylaxis later. For the same reason, cooked EW was used in this study; since it is better tolerated in EW allergic subjects (30). Other studies used raw egg (20).

This is the first randomized study considering oral desensitization in food allergic children. Groups were homogenous with regard to age, initial size of prick test wheals and specific IgE levels. Indeed, it is necessary to take into account children evolving without therapeutic intervention since tolerance can occur naturally. Hence, some children with negative results to 63 ml milk and 965 mg raw egg may have become

naturally tolerant. Only the difference in recovery rate of the two groups after 6 months will demonstrate any benefit of oral desensitization.

The rate of spontaneous recovery (60% for milk, 51.4% for egg), was significantly different from the rate of recovery obtained by oral desensitization (88.9%). Excellent results characterize CM IgE-mediated allergies: 90% vs. 54.5%. Gastrointestinal allergy had very favourable prognosis and may not require an oral tolerance protocol.

Oral desensitization to egg obtained a 69.4% rate of recovery versus 51.2% ($p < .1$). The trend might be better with a higher number of patients. Besides, knowing that failures usually occurred when the dose doubled from 2g to 4 g of cooked egg white, modifying the protocol by increasing the doses gradually over a longer period was thereafter successful (data not shown) (19-23).

In the group on avoidance diet, the comparison of cumulative reactive doses at the start of the study and after six months indicated that in certain cases, the threshold of reactivity was lowered: 9/12 for milk, 5/15 for egg. In some cases, the clinical signs presented during the second PCFC were more severe than those first seen and often at identical, or even lower, doses. Children in the avoidance group who initially presented only atopic dermatitis, experienced urticaria, angioedema, vomiting or lethargy (7 for egg and 2 for milk). Such cases have been published (31).

Significant immunological modifications are observed either after a period of avoidance or after the oral desensitization. In children on avoidance diets, an increase in the size of prick test wheals to milk had not been reported by previous studies. A decrease in prick test sizes after oral desensitization was noticeable (figure 3 and 4). Similarly, the oral desensitization to egg induced a significant decrease in the size of PT and a trend to decrease of specific IgE levels, even in cases of clinical failure (figure 5 and 6). This decrease has been observed in cured patients (9, 14) and by Patriarca after oral desensitization (22).

These results show first that avoidance may worsen the course of food allergies, creating an "oversensitization" for some children, that may be responsible for a more marked clinical reactivity (16). The reason for this phenomenon is unclear. An intermittent exposure to low amounts in the form of masked allergens or by inhalation of steam produced by cooking, might explain the growth of sensitivity (32). Even if the use of avoidance diets is a first-line treatment aiming to prevent anaphylaxis and to cure chronic disorders,

surely they are a temporary solution, needing to move towards immunotherapy or to an oral desensitization. Specific immunotherapy (IT) by injection has been used with some success (33). IT to pollens may improve the oral syndrome induced by cross allergy to fruit and vegetables (34). Attempts of IT to peanuts have failed (35). An attractive alternative is an oral desensitization: daily doses, gradually increasing are likely to create the conditions of an immune tolerance in the intestine. Indeed, the results obtained in the OD group indicate that a recovery of food allergies may be at hand by procedures of oral desensitization. A first attempt was proven successful as reported by Schloss in 1912 (18). Encouraging results for CMA (19-23, 36), egg (20-22), albumin (22), fish (22) and vegetable allergens have been published (22, 37-39). This study shows that oral desensitization over two months for milk or three months for egg appears to be beneficial in moderately allergic children. Moreover, it could be applied to children with severe and persistent milk allergy if the desensitization period is prolonged to 6 months, with a success rate of 71% according to Meglio (23).

CONCLUSION

The frequency of food allergy in children and the need to follow avoidance diets seriously affect the quality of life of children and of their parents. Spontaneous recovery is delayed and the duration of avoidance diets remains unknown. It could be argued that a new rationale should be adopted in allergy management. This randomized study has confirmed that avoidance, although protecting against severe anaphylactic reactions and necessary to relieve chronic symptoms, clearly involves a risk of increasing sensitization, and a risk of more severe clinical reactions. The implementation of oral desensitization resulted in significant recovery rates for milk, and recovery rates at the significance threshold for egg, showing that this procedure has lowered the sensitivity, and improved the evolution of allergies towards recovery. Further studies should confirm these data and investigate the mechanisms of the mucosal tolerance, since inducing gastrointestinal tolerance to foods by oral route is a promising approach, peanut allergy being not out of reach (40).

References

1. Sampson H.-A. - Improving in-vitro tests for the diagnosis of food hypersensitivity. *Curr Opin Allergy Clin Immunol* 2002;2:257-61.
2. Jakobsson I., Lindberg T. - A prospective study of cow's milk protein intolerance in Swedish infants. *Acta Paediatr Scand* 1979;68:853-9.
3. Host A., Halken S. - A prospective study of cow milk allergy in Danish infants during the first 3 years of life. *Allergy* 1990;45:587-96.
4. Schrandt JJP., van den Bogart JPH., Forget P.-P., Schrandt-Stumpel CTRM., Kuijten R.-H., Kester ADM. - Cow's milk protein intolerance in infants under 1 year of age: a prospective epidemiological study. *Eur J Pediatr* 1993;152:640-4.
5. Eggesbo M., Botten G., Halvorsen R., Magnus P. - The prevalence of CMA/CMPI in young children: the validity of parentally perceived reactions in a population-based study. *Allergy* 2001;56:393-402.
6. Eggesbo M., Botten G., Halvorsen R., Magnus P. - The prevalence of allergy to egg: a population-based study in young children. *Allergy* 2001;56:403-11.
7. Wood R.-A. - The natural history of food allergy. *Pediatrics* 2003;111:1631-37.
8. Bock S.-A. - The natural history of food sensitivity. *J Allergy Clin Immunol* 1982;69:173-7.
9. Boyano M.-T., Martin Esteban M., Pascual C., Ojeda J.-A. - Food allergy in children. II. Prognostic factors and long-term development. *An Esp Pediatr* 1987;26:241-5.
10. Host A., Halken S., Jacobsen H.-P., Christensen A.-E., Herskind A.-M., Plesner K. - Clinical course of cow's milk protein allergy/intolerance and atopic diseases in childhood. *Pediatr Allergy Immunol* 2002;13:23-8.
11. Bishop J.-M., Hill D.-J., Hosking C.-S. - Natural history of cow milk allergy: clinical outcome. *J Pediatr* 1990;116:862-7.
12. Hill D.-J., Heine R.-G., Cameron D.-J., Francis D.-E., Bines J.-E. - The natural history of intolerance to soy and extensively hydrolyzed formula in infants with multiple food protein intolerance. *J Pediatr* 1999;135:118-21.
13. Boyano-Martinez T., Garcia-Ara C., Diaz-Pena J.-M., Martin-Esteban M. - Prediction of tolerance on the basis of quantification of egg white-specific IgE antibodies in children with egg allergy. *J Allergy Clin Immunol* 2002;110:304-9.
14. Ford RPK., Taylor B. - Natural history of egg hypersensitivity. *Arch Dis Child* 1982;57:649-52.
15. Dannaeus A., Inganas M. - A follow-up study of children with food allergy. Clinical course in relation to serum IgE and IgG-antibody levels to milk, egg, and fish. *Clin Allergy* 1981;11:533-9.
16. Barbi E., Gerarduzzi T., Longo G., Ventura A. - Fatal allergy as a possible consequence of long-term elimination diet. *Allergy* 2004;59(6):668-9.
17. Leung D.-Y., Sampson H.-A., Yunginger J.-W., Burks A.-W. Jr, Schneider L.-C., Wortel C.-H., Davis F.-M., Hyun J.-D., Shanahan W.-R. Jr - Avon Longitudinal Study of Parents and Children Study Team. Effect of anti-IgE therapy in patients with peanut allergy. *N Engl J Med* 2003;348:986-93.
18. Schloss O. - A case of allergy to common foods. *Am J Dis Child* 1912;3:341-62.
19. Wuthrich B. - Oral desensitization with cow's milk in cow's milk allergy. *Pro! Monogr Allergy* 1996;32:236-40.
20. Patriarca G., Schiavino D., Nucera E., Schinco G., Milani A., Gasbarrini G.-B. - Food allergy in children: results of a standardized protocol for oral desensitization. *Hepatogastroenterology* 1998;45:52-8.
21. Patriarca G., Buonomo A., Roncallo C., Del Ninno M., Pollastrini E., Milani A., De Pasquale T., Gasbarrini G., Schiavino D., Nucera E. - Oral desensitization in cow milk allergy: immunological findings. *Int J Immunopathol Pharmacol* 2002;15:53-8.
22. Patriarca G., Nucera E., Roncallo C., Pollastrini E., Bartolozzi F., De Pasquale T., Buonomo A., Gasbarrini G., Di Campli C., Schiavino D. - Oral desensitizing treatment in food allergy: clinical and immunological results. *Aliment Pharmacol Ther* 2003;17:459-65.
23. Meglio P., Bartone E., Plantamura M., Arabito E., Giampietro P.-G. - A protocol for oral desensitization in children with IgE-mediated cow's milk allergy. *Allergy* 2004;59:980-7.

24. Moneret-Vautrin D.-A. - Food allergy: present problems and perspectives. In: *Advances in Allergology and Clinical Immunology*. Proceedings of the Vth EAACI, Paris. Ed Ph. Godard, J Bousquet, FB Michel, Parthenon Pub. 1992;473-83.
25. Rance F, Dutau G. - Labial food challenge in children with food allergy. *Pediatr Allergy Immunol* 1997;8:41-4.
26. Dreborg S. - Skin tests in diagnosis of food allergy. *Allergy Proc* 1991;12:251-4.
27. Moneret-Vautrin D.-A., Rance F, Kanny G., Olsewski A., Guéant J.-L., Dutau G., Guerin L. - Allergy to peanuts in France. Evaluation of 142 observations. *Clin Exp Allergy* 1998;28:1113-9.
28. Moneret-Vautrin D.-A., Kanny G., Beaudouin E., Morisset M. - Méthodologie des tests de provocation orale standardisés à double insu pour le diagnostic de l'allergie alimentaire. Revue de la littérature et expérience du service de Médecine Interne, Immunologie clinique et Allergologie. *Rev Fr Allergol* 2000;40:237-50.
29. Morisset M., Moneret-Vautrin D.-A., Guénard J.-L., Beaudouin E., Flabbée F., Hatahet R., Kanny G. - Thresholds of clinical reactivity to milk, egg, peanut and sesame in immunoglobulin E-dependent allergies: evaluation by double-blind or single-blind placebo-controlled oral challenges. *Clinical Exp Allergy* 2003;33:1046-51.
30. Romeira A.-M., Pires G., Gaspar A., Arede C., Morais-Almeida M., Rosado-Pinto J. - Egg allergy-to be or not to be boiled. *Allergy* 2003;58:533-4.
31. Flintermann A.-E., Meijer Y., Knulst A.-C., Bruijnzeel-Koomen CAF., Pasmans SGM. - Evaluation of the diagnosis of cow's milk allergy in children with atopic dermatitis. *Abstract book XXII congress of the EAACI* 2003;Abstr 632:187.
32. Roberts G., Golder N., Lack G. - Bronchial challenges with aerosolized food in asthmatic, food-allergic children. *Allergy* 2002;57:713-7.
33. Casimir G., Cuvelier P., Allard S., Duchateau J. - Life-threatening fish allergy successfully treated with immunotherapy. *Pediatr Allergy Immunol* 1997;8:103-5.
34. Lombardi C., Canonica G.-W., Passalacqua G. - Sublingual IT in OAS. *Allergy* 2000;55:677-8.
35. Oppenheimer J.-J., Nelson H.-S., Bock S.-A., Christensen F., Leung D.-Y. - Treatment of peanut allergy with rush immunotherapy. *J Allergy Clin Immunol* 1992;90:256-62.
36. Nucera E., Schiavino D., D'Ambrosio C., Stabile A., Rumi C., Gasbarrini G., Patriarca G. - Immunological aspects of oral desensitization in food allergy. *Dig Dis Sci* 2000;45:637-41.
37. Bauer A., Ekanayake Mudiyansele S., Wigge-Alberti W., Elsner P. - Oral rush desensitization to milk. *Allergy* 1999;54:894.
38. Rueff F., Eberlein-König B., Przybilla B. - Oral hyposensitization with celery juice. *Allergy* 2001;56:82-3.
39. De Pasquale T., Pollastrini E., Buonomo A., Roncallo C., Giuliani L., Lombardo C., Schiavino D., Nucera E., Patriarca G. - Desensitizing treatment of wheat allergy. *Abstract book XXII congress of the EAACI* 2003;Abstr 632:187.
40. Mansfield L. - Successful oral desensitization for systemic peanut allergy. *Ann Allergy Asthma Immunol* 2006;97:266-7.

