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Food Allergy: Oral Specific Desensitization

Eleonora NUCERA, Alessandro BUONOMO, Domenico SCHIAVINO, Massimiliano DEL NINNO, Giampiero PATRIARCA

Department of Allergology, Università Cattolica del Sacro Cuore - Policlinico Gemelli, Rome, Italy

SUMMARY

In the literature there are several conflicting reports dealing with the possibility of a desensitizing treatment in food allergy. In this paper we describe the methods and the results we obtained with an oral desensitizing treatment using standardized protocols.
The treatment was performed in 50 patients with food allergy (55 desensitizing treatments were carried out because some patients were allergic to more than one food). 11 patients did not continue the treatment, while 37 out of 44 successfully completed the program; at the end of the desensitization all patients who completed the treatment could eat the allergenic food with no side- effects at all.
So an oral desensitizing treatment should be taken into consideration in the management of food- allergic people.
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KEYWORDS

food allergy
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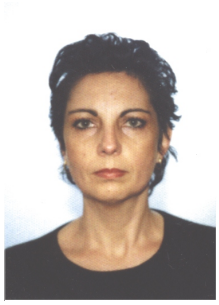
plant foods



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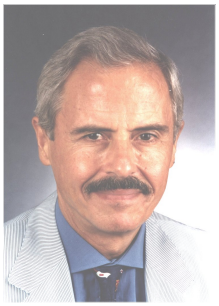

Giampiero Patriarca

Correspondence:
Prof. Giampiero Patriarca
Department of Allergology
Università Cattolica del Sacro Cuore-Policlinico Gemelli
L.go F. Vito, 1, I-00168 Rome, Italy

Phone: +39-(0)6-30154965
Fax: +39-(0)6-3051343
eMail: giapatr@tin.it

INTRODUCTION

The treatment of food allergy is still a hotly debated problem. The first therapeutic approach is to eliminate from the diet the allergenic food; this is not always possible because the food responsible could be an essential component of the diet (milk, egg) or it could be found in small amounts in other foods (for example milk in ice-creams, canned meat or fish, ham and sausages; eggs in alimentary paste and cakes) (Cantani 1999). Moreover, the elimination from the diet of foods such as milk or, to some extent eggs, could cause nutritional imbalances and growth problems in children.
A spontaneous desensitization, without any kind of therapy, but just with the avoidance of a food, may occur in 20-40% of patients who have eliminated the allergenic food from the diet, but it may take years (Bock 1982, Ford & Taylor 1982, Businco et al. 1985, Bock 1985, Wüthrich & Hofer 1986, Sampson & Scanlon 1989, Pastorello et al. 1989).
So a specific desensitizing should be taken into consideration as it regards food allergy too. The indications for a specific desensitizing treatment are (McEwen 1988):

- the impossibility of avoiding food exposure in the environment;
- the impossibility of following an elimination diet that could be socially discriminating, too expensive or lacking from the nutritional point of view;
- the impossibility of maintaining an adequate diet regimen in patients allergic to several foods.

A desensitizing treatment via the subcutaneous route has been carried out in the past (Pasteur & Blaumoutier 1956, Sheldon et al. 1967, Goldstein & Heiner 1970, Tuft & Muller 1970, Rowe & Rowe 1972) with important side- effects and poor results, even if recently good results have been reported as regards peanut allergy (Shenassa et al. 1985, Oppenheimer et al. 1992, Nelson et al. 1994).

In our opinion attention should be paid to specific oral desensitization, even if in the literature there are conflicting reports. In 1912 Schloss reported a successful oral desensitizing treatment in a child with egg allergy; in 1920 he described 12 cases of patients with milk allergy treated successfully with oral desensitization (Schloss 1920). Recently, various reports have appeared in the literature regarding oral specific desensitization: Pasteur & Blamoutier (1956), Vaillaud et al. (1969), Wüthrich & Hofer (1986), Schiavino et al. (1990), Patriarca et al. (1984, 1998) and Wüthrich (1996) report positive results while Fontana (1969), Goldstein & Heiner (1970), Rowe & Rowe (1972), May et al. (1978) and Bahna (1996) report negative results. These conflicting results are due to the fact that generally standardized desensitizing protocols have not been adopted.

We report in this work the results we obtained with oral specific desensitization in patients with food allergy who underwent this treatment according to standardized protocols (Patriarca et al. 1984, Schiavino et al. 1990, Patriarca et al.1998) (Tables 2-4).

MATERIAL & METHODS

Patients
We investigated as outpatients of our Department of Allergology 50 subjects (29 females and 21 males) with food allergy, aged from 3 to 55 years.
The diagnosis of food allergy was made on the basis of the clinical history and a complete allergological evaluation: a) skin prick tests using at first allergens supplied by the pharmaceutical industry and then fresh foods (prick by prick method) - a wheal and flare reaction (more than 3 mm in diameter) together with a negative control skin prick test was considered as positive; b) measurement of total (PRIST Pharmacia) and specific IgE (RAST Pharmacia) was considered positive for values of specific IgE higher than 3.5 kU/L (class 3); specific IgE were detected for alpha-lactalbumin, beta-lactoglobulin, and casein as regards milk, and for albumen and yolk as it regards egg; c) double-blind placebo- controlled food- challenge (DBPCFC).
The patients who underwent a desensitizing treatment all had a positive DBPCFC; for skin prick test and RAST results see Table 1.

Table 1: Skin prick test and RAST results in 50 patients with food allergy

Patients	**Sex and age** (years)	**Food**	**Skin prick test results** (for 1 or more allergens)	**RAST results** (for 1 or more allergens)
FE	F, 14	Apple	Positive	Negative
AA	M, 21	Milk	Positive	Positive
GS	M, 7	Egg	Positive	Negative
SA	F, 19	Milk	Negative	Positive
SI	F, 5	Milk	Positive	Positive
BG (this patient underwent a desensitizing treatment twice)	F, 30	Milk	Positive	Positive
ME	M, 28	Fish	Positive	Positive
VS	M, 14	Beans	Positive	Positive
RA	F, 13	Milk	Positive	Positive
RM	F, 38	Fish	Positive	Positive
RS	F, 6	Milk, Egg albumen, Fish	Positive, Positive, Positive	Positive, Positive, Positive
GM	M, 6	Milk	Positive	Positive
LG	M, 11	Milk	Positive	Positive
RD	F, 21	Orange, Lettuce	Positive, Positive	Positive, Not done
FS	F, 27	Milk	Positive	Positive
SR	F, 24	Milk	Positive	Negative
SS	F, 22	Peach	Positive	Negative
AB	F, 5	Milk	Positive	Positive
PS	M, 19	Egg	Positive	Positive
VR	M, 3	Milk	Positive	Positive
AE	F, 20	Orange	Positive	Negative
LM	M, 29	Egg	Positive	Positive
DMC	F, 44	Milk	Positive	Negative
CE	F, 5	Egg	Positive	Positive
CF	M, 25	Fish	Positive	Positive
GP	M, 16	Fish	Positive	Positive
MG	M, 6	Egg	Positive	Positive
BM	M, 12	Egg	Positive	Positive
DGE	F, 11	Milk	Positive	Positive
MF	M, 26	Fish	Positive	Positive
PA	F, 23	Milk	Positive	Positive
DPG	F, 25	Milk, Egg	Positive, Positive	Negative, Negative
CL	M, 32	Egg	Positive	Positive
GD	F, 31	Egg	Positive	Positive
CG	F, 34	Milk	Positive	Negative
TM	F, 37	Egg	Positive	Negative
VD	M, 43	Milk	Positive	Positive
MM	F, 55	Milk	Positive	Negative
LJ	F, 30	Peanut	Positive	Positive
CI	M, 13	Fish	Positive	Positive
BS	F, 11	Egg	Positive	Positive
VC	F, 4	Egg	Positive	Positive
VS	F, 4	Milk	Negative	Positive
CA	F, 10	Egg albumen	Positive	Negative
NA	M, 5	Milk	Positive	Positive
VE	M, 8	Egg	Positive	Positive
AA	M, 7	Egg albumen	Positive	Positive
ZC	F, 8	Milk	Positive	Positive
VV	F, 49	Corn	Positive	Positive
LG	M, 11	Milk	Positive	Positive

We diagnosed 24 milk allergies, 16 egg allergies, 7 fish allergies, 2 orange allergies and other 6: apple, beans, peach, lettuce, peanut and corn (some patients were allergic to more than one food). The patients with fruit, nut and vegetable allergy did not suffer from a pollinosis and so an oral allergy syndrome could be excluded.

DBPCFC

The DBPCFC was done administering the allergen (milk, apple shake, shaken egg, etc.) diluted in 50 mL vanilline or using opaque capsules for cod. Vanilline and talc capsules alone were used as placebos.
The DBPCFC was performed on two days, with a three-day interval, administering the placebo and the allergen at increasing doses every 30 minutes: for milk, egg, apple, peach, orange, etc. doses of 0.01, 0.1, 1, 2, 5, 10 and 20 mL were administered; as regards cod, the doses were of 0.005, 0.05 0.5, 1, 2, 5, 10 and 20 g.
The test was interrupted if any reaction occurred. After the DBPCFC, the patients were followed for 8 hours and they had to record any reaction in a diary.
The DBPCFC was considered positive if one of these reactions occurred:

- urticaria/angioedema or erythema with pruritus;
- rhinitis, rhinorrhea, nasal obstruction and asthma;
- vomiting, diarrhea or abdominal pain;
- general malaise, lipothymia.

Oral Desensitization

All patients underwent an oral desensitizing treatment; the patients who were allergic to more than one food underwent one desensitizing protocol at a time; moreover a patient already desensitized with milk was desensitized again, since she had not drunk milk for years, losing the state of tolerance.
So an oral desensitizing treatment was performed 55 times, according to our standardized protocols: at first a diluted food was administered and then we administered the pure food at increasing doses. The starting dilutions used for the desensitization protocols were lower than those used for the DBPCFC. Sometimes, at the beginning of the treatment, sodium chromoglycate (SCG) (250 or 500 mg, according to the patient's age) was administered 20 minutes before food ingestion; if no reactions occurred, this pretreatment was dropped out in a few days.
After completing the treatment, we told all patients to continue eating the allergenic food approximately twice a week, so as not to lose the state of tolerance.

Table 2: Oral specific desensitization in patients allergic to milk (Patriarca et al. 1998)

Starting dilution: 10 drops of milk in 10 mL of water	
Days 1 to 3	4 drops
Days 4 to 6	6 drops
Days 7 to 9	10 drops
Days 10 to 12	12 drops
Pure milk	
Days 13 to 15	1 drop
Days 16 to 18	2 drops
Days 19 to 21	4 drops
Days 22 to 24	6 drops
Days 25 to 27	10 drops
Days 28 to 30	16 drops
Days 31 to 33	32 drops
Days 34 to 36	48 drops
Days 37 to 40	40 drops x 2
Days 41 to 44	40 drops x 3

Pure milk	
Days 45 to 48	40 drops x 4
Days 49 to 52	50 drops x 4
Days 53 to 56	60 drops x 4
Days 57 to 60	4.5 mL x 3
Days 61 to 64	5 mL x 3
Days 65 to 68	6 mL x 3
Days 69 to 72	5 mL x 4
Days 73 to 76	6 mL x 4
Days 77 to 80	7 mL x 4
Days 81 to 84	9 mL x 4
Days 85 to 88	12 mL x 4
Days 89 to 92	15 mL x 4
Days 93 to 96	15 mL x 5
Days 97 to 100	30 mL x 3
Days 101 to 104	50 mL x 2
Maintenance dose: 100 ml 2-3 times a week	

Table 3: Oral specific desensitization in patients allergic to egg (Patriarca et al. 1998)

Starting dilution: 10 drops of shaken egg* (albumen and yolk) in 100 mL of water	
Days 1 to 3	4 drops
Days 4 to 7	4 drops x 2
Days 8 to 11	4 drops x 3
Days 12 to 14	8 drops x 3
Days 15 to 17	16 drops x 3
Days 18 to 20	36 drops x 3
Pure shaken egg*	
Days 21 to 23	1 drop
Days 24 to 26	2 drops
Days 27 to 29	3 drops
Days 30 to 32	4 drops
Days 33 to 35	6 drops
Days 36 to 38	12 drops
Days 39 to 41	10 drops x 2
Days 42 to 44	10 drops x 3

Pure shaken egg*	
Days 45 to 47	15 drops x 3
Days 48 to 50	20 drops x 3
Days 51 to 53	25 drops x 3
Days 54 to 56	35 drops x 3
Days 57 to 59	50 drops x 3
Days 60 to 62	5 mL x 2
Days 63 to 65	5 mL x 3
Days 66 to 68	5 mL x 4
Days 69 to 71	10 mL x 3
Days 72 to 74	10 mL x 4
Days 75 to 77	15 mL x 3
Days 78 to 81	15 mL x 4
Days 82 to 85	15 mL x 5
Days 86 to 90	30 mL x 3
Maintenance dose: 1 egg 2-3 times a week	

* : an homogeneous dilution was obtained by shaking one egg for 3 minutes

Table 4: Oral specific desensitization in patients allergic to fish (Patriarca et al. 1998)

Starting dilution: 10 mL of 6% fish extract* (Lofarma allergeni, Milan) in 90 mL of water	
Days 1 to 3	4 drops
Days 4 to 6	8 drops
Days 7 to 9	12 drops
Days 10 to 12	24 drops
Days 13 to 15	32 drops
Days 16 to 18	48 drops
Days 19 to 21	72 drops
Days 22 to 24	108 drops
Pure fish extract	
Days 25 to 27	15 drops
Days 28 to 30	30 drops
Days 31 to 33	45 drops
Days 34 to 36	60 drops
Days 37 to 39	5 mL
Days 40 to 42	10 mL
Days 43 to 45	15 mL
Cooked fish (boiled cod)	
Days 46 to 48	1 g
Days 49 to 51	2 g
Days 52 to 54	3 g
Days 55 to 57	4 g

Cooked fish (boiled cod)	
Days 58 to 60	5 g
Days 61 to 63	6 g
Days 64 to 66	8 g
Days 67 to 69	10 g
Days 70 to 72	12 g
Days 73 to 75	15 g
Days 76 to 78	18 g
Days 79 to 81	22 g
Days 82 to 84	27 g
Days 85 to 87	32 g
Days 88 to 90	40 g
Days 91 to 93	48 g
Days 94 to 96	56 g
Days 97 to 99	64 g
Days 100 to 102	72 g
Days 103 to 105	95 g
Days 106 to 108	110 g
Days 109 to 111	130 g
Days 112 to 114	150 g
Days 115 to 117	175 g
Days 118 to 120	200 g
Maintenance dose: 200 g of boiled fish almost once a week	

**** : 1.5% eel, 1.5% cod, 1.5% sardine, 1.5% anchovy***

RESULTS

11 patients dropped out because of lack of compliance, while in 7 cases we decided not to continue the treatment since we could not increase the doses because of the side- effects: diarrhoea, vomiting, abdominal pain we could not control even by administering SCG or antihistamines per os before food ingestion.

37 of the remaining 44 patients (84.1%) successfully completed the treatment and could eat currently the food they were allergic to; so we decided not to repeat the DBPCFC.

During the treatment 18 patients out of 44 (40.9%) showed slight side- effects such as urticaria, angioedema and abdominal pain, well controlled with an antihistamine therapy per os.

Specifically, we had the following results (Table 5):

- as regards milk allergy (24 cases), the treatment was completed in 3-8 months in 16 cases; in 5 cases it was abandoned by the patients while in 3 we decided to stop;
- as regards egg allergy (16 cases), the treatment was completed in 11 cases in 3-7 months; in 2 cases it was abandoned by the patients while in 3 we decided to stop (2 out of the 12 patients who successfully completed the treatment, underwent an oral desensitization with egg albumen only, since they were not allergic to yolk proteins; in fact the DBPCFC with egg yolk was negative);
- as regards fish allergy (7 cases), the treatment was completed in 5 cases in 4-10 months; in 1 case it was abandoned by the patients and in 1 we decided to stop;
- as it regards orange (2 cases), apple (1 case), corn (1 case) and peach (1 case) allergies, the treatment was completed in 3-7 months;
- as regards peanut (1 case), bean (1 case) and lettuce (1 case) allergies, the treatment was abandoned by the patients.

The different length of time of the treatments for the same foods is due to the fact that sometimes we had to proceed slowly because of the occurrence of mild side- effects.

DISCUSSION

The possibility to obtain an oral desensitization in patients with drug allergy is widely accepted, even if the mechanism is still debated. In contrast, the possibility to obtain an oral desensitization in patients with food allergy has always been considered with interest, but also with scepticism (Burks et al. 1995).
In the literature there are several reports that deal with the possible physiopathogenetic mechanism of oral desensitization, but the exact mechanism is still unknown; in fact some hypotheses have been made (Strobel 1997): a) antigen- driven suppression; b) clonal anergy; c) clonal deletion.
The fact that the phenomenon of tolerance may be involved in the mechanism of desensitization is still uncertain (Lowney 1968, Tomasi et al. 1983, Bellanti 1984).

So, to better understand the immunological mechanism of oral desensitization, we studied the immunological state of one of the treated patients with milk allergy at the beginning, during and at the end of the treatment (Nucera et al. 2000). Before starting the treatment, ECP (eosinophil cationic protein), tryptase, specific IgE, IgA and IgG, IL-4 and IFN-gamma in serum and in the supernatant of mononuclear blood cells stimulated with phytohemoagglutin and with phorbol- myristate acetate or with beta-lactoglobulin were detected.

Table 5: Results of oral desensitization

Food	Cases	Results
Milk	24	Positive: 16 Negative:3 Interruptions: 5
Egg	16	Positive: 11 Negative: 3 Interruptions: 2
Fish	7	Positive: 5 Negative: 1 Interruptions: 1
Orange	2	Positive: 2
Peach	1	Positive: 1
Apple	1	Positive: 1
Corn	1	Positive: 1
Bean	1	Interruptions: 1
Peanut	1	Interruptions: 1
Lettuce	1	Interruptions: 1
Total	**55**	**Positive: 37** **Negative: 7** **Interruptions:11**

The skin prick tests, at the beginning positive for milk, casein, alpha-lactalbumin and beta-lactoglobulin turned negative after 7 months; specific IgE directed against milk proteins decreased, while we observed an increase of serum specific IgG and IgA. Moreover we observed a reduction in the production of IL-4 both in vitro and in serum and an increase in the production of IFN-gamma by T lymphocytes, both spontaneously and after stimulus with beta-lactoglobulin.
These results make us think that during oral desensitization a switch from a Th2 response (with production of IL-4, IL-3, IL-5 and IL-13) to a Th1 response (with production of IL-2 and IFN-gamma) may occur, as it has been observed during specific immunotherapy for respiratory allergic diseases. Such measurements are already in preparation for other patients.

Recently, new therapeutical approaches have appeared in the literature as regards food allergy. In a murine model it has been observed that the oral administration of chitosan-DNA nanoparticles, which codify for the allergen Ara h 2 of peanut, induce the production of secretory IgA and seric IgG2a directed against that allergen; so the animal was protected towards new episodes of anaphylaxis caused by that food (Krishnendu et al. 1999). In a previous work it has been demonstrated that the oral administration of ovalbumin linked to isologous IgG induce an allergen specific suppression of both lymphocytes B and T in rats (Borel et al. 1995).

In this paper we used standardized protocols for oral desensitization in food allergic people; the application of such protocols allowed us to obtain 84.1% success in patients who completed the treatment. Few side-effects occurred and the safety of the treatment was increased by using SCG in some patients in the early phase of the treatment. No hospitalization is needed and the desensitization can be carried out in an out-patient regimen.
It is very unlikely that the results we obtained could be due to a spontaneous desensitization, since this phenomenon generally takes years and avoidance of the allergenic food is needed while our patients ate the allergenic food every day.

In conclusion, oral desensitization should be taken into consideration in the management of food- allergic patients even if the physiopathogenetic mechanisms have still not been explained completely. Moreover, this treatment should be considered especially for children since for these patients the elimination from the diet of some foods (milk, egg) could cause psychological and/or nutritional problems.

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[Summary] [Abbreveations]