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Specific oral tolerance induction for food. A systematic review

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KEY WORDS

Food allergy, oral desensitization

SUMMARY

Background: Specific oral tolerance induction (SOTI) is a new therapeutic approach in the treatment of persistent food allergy. **Objective:** The purpose of this article is to systematically review the literature in order to identify, appraise, and synthesize the evidence about SOTI efficacy and safety. **Methods:** A comprehensive search for citations was conducted on May 2, 2009 using MEDLINE via PubMed. Randomized controlled trials (RCTs) including subjects of any age were considered. All these studies were assessed, discussed in details and evaluated for quality by authors in a standardized independent way. **Results:** 15 clinical trials were found. Of these, six trials met the inclusion criteria: three were open label RCT, three were double blind placebo controlled RCT. Two were conducted using sublingual immunotherapy, four using oral desensitization. Overall, the methodological quality of the studies was sufficient. The mean Jadad score of the studies was 3,33 (range = 2-5). Main characteristics and results of the studies were showed and discussed. **Conclusions:** SOTI seems to be a possible approach to accelerate the development of tolerance in children affected by food allergy. However, other studies are needed to clarify which is the best treatment and protocol to follow in order to reduce the adverse events and to increase the percentage of success, before thinking that SOTI might be part of the clinical practice.

Background

Until few years ago, the treatment of food allergies consisted in avoiding the ingestion of food responsible of specific symptoms (elimination diet), in recognizing early symptoms of an allergic reaction in cases of accidental ingestion, and in starting the appropriate emergency therapy. Food allergies' natural history showed that they generally tend to heal spontaneously with time, but tolerance seems to occur faster in cow's milk or egg allergy, and later, or sometimes never, in fish or peanut allergy.

Recently, some studies have demonstrated that food allergies' natural history seems to be less favourable, even for

those food allergies considered to have a good prognosis. In a prospective population study (6205 newborns enrolled) Saarinen showed that more than 15% of the 118 children with IgE mediated cow's milk protein allergy (CMPA) did not tolerate milk at the age of 8.6 years (1). More recently, Skripak has carried out a retrospective study on 807 selected children affected by CMPA, demonstrating that tolerance may occur even later: only 42% of children tolerated milk at the age of 8 years, and 79% at the age of 16 years (2). Therefore food allergies persist in some children, and to keep a special diet may become heavier and heavier, with significant psychological and nutritional implications. In clinical practice following an elimination diet over the years

is almost impossible: most of children can occasionally and inadvertently intake food they are allergic to, sometimes going through unexpected and serious reactions. Moreover some foods commonly responsible of food allergies, such as egg and milk, are frequently found in small amounts in food trade, and they are not always declared.

The dogma that a strict elimination diet is the only way to develop tolerance has been recently put in doubt (3). Some studies have demonstrated that recurrence of peanut allergy was more probable in those subjects who broke off the peanut intake after they got tolerance, than in those who continued assuming peanut more regularly (4); this finding suggests that, instead of the strict elimination diet, the continuous administration of the food can facilitate the development and maintenance of tolerance.

Thereby a return of interest in the practice of food desensitization has come out. Subcutaneous desensitization has already been tried several years ago, but it was soon abandoned after the results of Oppenheimer (5) and Nelson (6). In these studies frequent and severe desensitization side effects were shown: this treatment was able to significantly reduce sensitization to peanuts (5 out of 6 treated subjects vs none of the control subjects), but continuing the administration of the therapy became impossible in half of the treated subjects because of recurrences of systemic reactions. In all treated patients administration of epinephrine was needed during the induction phase, and in five out of six of them also in the maintenance phase: the treated subjects received on average 7.7 doses of epinephrine, one of them even received 39 doses!

On the contrary, specific oral tolerance induction (SOTI), proposed and carried out since about 20 years ago (7), seems to be weighted by fewer side effects and therefore is now put under new interest.

SOTI, oral desensitization and oral/sublingual immunotherapy are likewise used by several authors to define this treatment.

However, according with the WHO Position paper, allergen immunotherapy consists in the administration of gradually increasing quantities of an allergen vaccine to an allergic subject, reaching a dose which is effective in ameliorating the symptoms associated with subsequent exposure to the causative allergen (8). On the contrary, allergen desensitization consists in the continuous administration of incremental doses of an allergen or allergenic substance, reaching a total dose needed for drug treatment or food nutrition.

These 2 treatments could differ from each other. In fact they seem to subtend different immunologic mechanism;

for example oral desensitization done with drugs does not induce a long-lasting immunological tolerance, probably because it produces an IgE block more than a real change of the immune response (9).

The purpose of this article is to systematically review the literature in order to identify, appraise, and synthesize the evidence of SOTI efficacy and safety, underlieng the possible different approaches.

Throughout this article, the terminus specific oral tolerance induction (SOTI) was used for consistency.

Methods

Search strategy

A comprehensive search for citations was conducted on May 2, 2009 using MEDLINE via PubMed. To reduce the risk of losing relevant studies, searches were not restricted by language of publication, publication type, or study design. Index terms for “oral desensitization and food allergy”, “immunotherapy and food allergy” and “specific oral tolerance induction and food allergy” were used.

We have extended our search for relevant studies looking through:

- the Cochrane Controlled Trials Register
- the references of some reviews published on this topic (10, 11)
- the references of the clinical studies identified as relevant
- hand searching of the last two-year indexes of: Allergy, Annals of Allergy Asthma and Immunology, Clinical and Experimental Allergy, Pediatric Allergy and Immunology, The Journal of Allergy and Clinical Immunology, Archives of Disease in Childhood, Pediatrics, The Journal of Pediatrics

Randomized controlled trials (RCT's) on subjects of any age were included. All these studies were assessed, discussed in details and evaluated for quality by the authors of this review in a standardized independent way.

Given the few data on this topic available in literature, we have also included a brief report about all clinical trials found, even if not randomized and controlled.

Exclusion criteria

Studies published only as abstracts were excluded. Moreover, other studies were excluded if drop out during fol-

low up was 20% or more of randomised patients (12) or if the subjects included in the study was lower than 10.

Methodological quality of the included studies

The methodological quality of the included studies was evaluated according to the criteria given by the Evidence-Based Medicine Working Group (12). In each study the following items were analysed: the randomisation process; the efficacy of randomisation (through the analysis of the RCT table where authors summarize patients general characteristics about sex, economic status, age et al.); sample size calculation; definition of end points; drop out or lost during follow up; compliance; intention to treat analysis; placebo concealment; run in. Then the Jadad score was calculated for each study (13).

Results

The search with the term “oral desensitization and food allergy” revealed 82 articles, the search for “immunotherapy and food allergy” gave 917 articles, and the other one for “specific oral tolerance induction and food allergy” gave 54 articles. No other studies were found throughout the other search.

We found 15 clinical trials. Of these, six trials met the in-

clusion criteria: three were open label RCT, three were double blind placebo controlled RCT. Two were conducted using sublingual immunotherapy (SI), four using oral desensitization (OD) (Tab. 1).

Overall, the methodological quality of the studies was sufficient. All studies had a drop out lower than 20% of randomised patients. Only 1 study (14) achieved the maximum Jadad score; the mean Jadad score of the studies was 3,33 (range = 2-5) (Tab. 2).

A quantitative evaluation was not possible because outcomes and results were described according to different criteria. Only qualitative analysis was performed.

Eight studies were excluded because they were open trials with (15) or without (16-21) a control group, or cases series (22). One RCT was excluded because only 13 children were enrolled, and only six of them were randomized to a double blind desensitization to milk (23). Main characteristics and results of the studied excluded are showed in table 3.

Description of the results of each clinical study

Sublingual immunotherapy

Enrique (24) enrolled 29 allergic adults to hazelnut. After randomization, a sublingual solution containing the major

Table 1 - Main characteristics of the studies enclosed in the analysis

Author	Treatment	Design	Age	Cases (n.)	Controls (n.)	Food	Level of Evidence
Enrique, 2005	Sublingual Immunotherapy	RCT-DB	Adults	12	11	Hazelnut	1b-
Fernandez Rivas, 2009	Sublingual Immunotherapy	RCT-DB	Adults	37	19	Peach (Pru p-3)	1b-
Morisset, 2007	Oral desensitization	RCT	Children (mean age 2.2 yrs and 3.5 yrs for milk and egg, respectively)	27 (milk) and 49 (egg)	30 (milk) and 35 (egg)	Milk/egg	1b-
Staden, 2007	Oral desensitization	RCT	Children (mean age 2.5 yrs)	25	20	Milk / egg	1b-
Longo, 2008	Oral desensitization	RCT	Children (mean age 7.9 yrs)	30	30	Milk	1b-
Skripak, 2008	Oral desensitization	RCT-DB	Children (mean age 10 yrs)	13	7	Milk	1b-

Table 2 - Methodological quality of the studies according to the Jadad score

Jadad score	Enrique	Fernandez-Rivas	Morisset	Staden	Longo	Skripak
Is the study described as randomized?	1	1	1	1	1	1
Was the randomization method appropriate?	0	1	1	0	1	0
Was the study described as double blind?	1	1	0	0	0	1
Is the blindness method described and appropriate?	1	1	0	0	0	0
Is there a description of the lost at follow-up and of the excluded subjects?	1	1	1	1	1	1
Remove one point if the method used to generate the randomization sequence was not appropriate	0	0	0	0	0	0
Remove one point if the study was described as double blind but the method used was not appropriate	0	0	0	0	0	0
Overall Jadad score	4	5	3	2	3	3
Mean Jadad score	3,33					

Table 3 - Main characteristics and results of the studies excluded from analysis

Author	Treatment	Design	Age	Cases (n.)	Controls (n.)	Food	Adverse effect	Failure (%)
De Boissieu, 2006	SI	Open	Children (over 6 yrs)	8	-	Milk	12,5	50
Wuthrich, 1996	OD	Open	Adult	16	-	Milk	?	25
Patriarca, 2003	OD	Open controlled	Children and adult (3-55 years)	59	16	Milk (29), egg (15) fish (11) other foods (6)	67,8	16,7
Longo, 2004	OD	Open	Children (mean age 6.8 yrs)	30	-	Milk	100	10
Meglio, 2004	OD	Open	Children (median age 6 yrs)	21	-	Milk	62	14,2
Buchanan, 2007	OD	Open	Children (14-84 months)	7	-	Egg	100	43
Zapatero, 2008	OD	Open	Children (mean age 5 yrs)	18	-	Milk	68,5	11,4
Staden, 2008	OD	Open	Children (3-14 yrs)	9	-	Milk	100	33,3
Caminiti, 2009	OD	RCT (in a subgroup)	Children (mean age 8 years)	3 (+ 7 in open)	3	Milk	80	20

antigen of hazelnut or a placebo was double-blinded administered. The protocol provided for taking 1 drop of the solution, which was to be retained in the mouth at least 3 minutes and then spat out; the number of drops was increased every 15 minutes up to 10 drops per day. The drops contained increasing concentrations of the standardized hazelnut solution, up to 2.6 mg of hazelnut. The highest drops' dose was reached after 4 days, then the patient was discharged and continued the therapy at home taking 5 drops per day. The follow-up consisted in medical visits to be performed every 3 weeks for 3 months. Then an oral food challenge and the dosage of specific IgE level were performed. The aim of this study was to evaluate the possibility of reaching tolerance to hazelnut, and to describe the changes in the maximum tolerated dose by performing a double blind placebo controlled food challenge (DBPCFC) before and 8-12 weeks after treatment. Six out of the 29 subjects enrolled refused to participate. Of the remaining 23, 12 were randomized to the active group and 11 to the placebo group. One patient of the treated group dropped out at the beginning of the study. At the end of the treatment plan, 5/11 (45.4%) of patients vs 1/11 (9%) of controls tolerated an amount of 20 gr. of hazelnut (about 15-20 hazelnut). The average amount tolerated increased from 2.3 gr. to 11.3 gr. in the treated group, while it increased from 3.5 gr. to 4.1 gr. in the placebo group. Three systemic reactions (in the 0.2% of the 1466 doses administered) were described during treatment: one facial urticaria in the placebo group and two urticaria manifestations in 1 patient of the treated group. Local reactions, such as oral pruritus, were described in 109/1466 (7.4%) doses.

Fernandez Rivas (14) enrolled a group of adults with peach allergy, immediate reaction and positive SPT or specific IgE. The diagnosis was made after a positive DBPCFC, which was considered positive after the first clinical sign or after 3 consecutive doses in which an unequivocal oral allergy syndrome was shown. The cumulative dose of Pru p 3 given during DBPCFC was 3249 mcg, corresponding to 200 g of pit-less unpeeled peach.

Of 76 screened patients, 52 were enrolled and randomized in a 2:1 proportion to the group of SI (37 patients) or the control group (19 patients). The immunotherapy schedule comprises a build-up phase of two week in the hospital and a home maintenance phase of six months. During the first phase the treatment was administered sublingually (sublingual-swallow technique) starting with 0,22 mcg of Pru p3 in the first day, increased to 50 mcg in the fifth day. During the home maintenance phase a dose

of 10 mcg/die of Pru p3 was administered three days a week. After 6 months the DBPCFC and the allergy-tests were repeated. Forty-nine patients completed the trial, 33/39 of the SI group and 16/19 of the placebo group. One subject was unable to take the dose of 10 mcg, and carried out a maintenance with the dose of 2 mcg. In the placebo group no differences in doses that could determine local or systemic reactions were observed, while doses able to determine local reactions or systemic reactions in the SI group increased of 9 and 3 times respectively. About safety, reactions occurred after the administration of 1356 out of 1480 doses administered. Systemic reactions occurred in 16 cases, none was severe.

Oral desensitization

The study of **Morisset** included a population of 150 children, 60 with cow's milk proteins allergy (CMPA) and 90 with egg allergy (25). The diagnosis of food allergy was made on the basis of the presence of sensitization, Skin Prick Test (SPT) or specific IgE, and confirmed by a positive result to the placebo controlled oral challenge. Only subjects reactive to >60 ml of cow's milk or >965 mg of white raw egg were enrolled to exclude the most sensitive patients. After 6 months of desensitization, SPT or specific IgE and the oral challenge were performed again in order to assess tolerance. The protocol provided a slow administration of cow's milk, starting with 1 ml on the first day, increasing to 20 ml the 1 week, then to 50 ml the second week, to 100 ml the third, to 250 ml the sixth. A similar dose increasing protocol was used for those children with egg allergy.

Among the children with CMPA, 3/27 (11,1%) had to stop OD because of clinical reactions, while the remaining 24/27 (89.9%) tolerated up to 200 ml of cow's milk; in the control group, 12/30 (40%) were still allergic ($P < 0.05$), and 7/12 reached lower cumulative reactive doses than that used in the first DBPCFC, and there were more severe symptoms. The drop out was 10%.

Among children with egg allergy, 15/49 (30.6%) had to stop OD because of clinical reactions, while the remaining 34/49 (69.4%) tolerated up to 4 gr. of yolk and 4 gr. of albumen every other day. In the control group 17/35 (48.6%) of the children were still allergic ($P = 0.1$) and 9/17 had a positive challenge test to lower doses of egg and more severe symptoms. The drop out was 6.6%.

Staden enrolled 45 children with cow's milk and egg allergy (26). The diagnosis of food allergy was made on the basis of the presence of sensitization (SPT or specific

IgE) and confirmed by a positive result to DBPCFC. Children were randomized in two groups, one received OD (25 children, 14 allergic to cow's milk, 11 to egg), and one received placebo (20 children, 10 allergic to cow's milk, 10 to egg). All children were reassessed by DBPCFC after 18-24 months of treatment. Moreover, children who underwent OD were reassessed after a period of secondary elimination diet of 2 months, in order to evaluate the persistence of tolerance. The OD was performed at home with lyophilized milk or egg, with starting doses of 0.02 mg of milk proteins and 0.006 mg of egg proteins; the doses were then slowly (in about two months) increased up to 8250 mg of milk (250 ml) or 2800 mg of egg (half of an egg). Then the patient continued to assume a minimum of 100 ml of milk or around $\frac{1}{2}$ an egg. At the end of the study (after an average of 21 months), 16/25 (64%) children tolerated milk: of these, 9 (36%) tolerated a free diet, 4 (16%) tolerated only low doses of milk, and 3 (12%) had new reactions after the secondary elimination diet, while 9 (36%) continued to be allergic. In the control group 7/20 (35%) developed tolerance. All children treated with OD didn't have side effects during the study. Twenty-one children showed mild symptoms of allergy, 4 had more severe symptoms and required the administration of steroids and antihistamines. In **Longo's** study (27) 97 children with CMPA and history of severe allergic reactions and of specific IgE levels > 85 KU/l were selected. CMPA was diagnosed by DBPCFC performed at the beginning and at the end of the study. Sixty children were then enrolled and randomized to OD (30 children) and placebo (30 children). Children started treatment in the hospital where they were admitted for 10 days: here very diluted and gradually increased doses of cow's milk were administered, up to achieve the administration of 20 ml of milk. Then the treatment was continued at home, and doses were increased of 1 ml every other day to reach the maximum dose of 150 ml. At the end of the first 10 days, 9/30 (30%) reached the dose of 20 ml, while the remaining reached lower doses of milk because of frequent allergic reactions, which obliged them to change or stop the protocol. After 1 year, 11/30 (36%) children achieved tolerance for 150 ml and a free diet, 16/30 (54%) tolerated lower doses of cow's milk (between 5 and 150 ml), while 3/30 (10%) had to stop OD. All controls did not tolerate milk at the DBPCFC performed after 12 months. All children virtually showed reactions during OD. During the first 10 days in the hospital 4 (13.3%) children required the administration of IM epinephrine and 18 children aerosolised epinephrine. During

the protocol phase performed at home 4 children required epinephrine. 20% children of the control group had clinical reactions during the study: all of them were mild.

Skripak is the author of the only DB-RCT with milk enrolling 20 children with CMPA (28). Children with a history of anaphylaxis or severe-persistent asthma or who had required intubation were excluded. The diagnosis of CMPA was made by DBPCFC at the beginning and at the end of the study. After recruitment 2/3 (n. 13) of children were randomized to the OD and 1/3 (n. 7) to placebo. The treatment began with the dose of 0.4 mg of milk protein with daily increases up to 50 mg (1.5 ml); the increases were made every 1-2 weeks in order to reach the dose of 500 mg (15 ml). Then this dose (15 ml) was continued for other 13 weeks. After 23 weeks DBPCFC was again performed. Those children who tolerated after treatment less than 2540 mg (about 70 ml) were again put on diet. The median maximum dose tolerated before the OD was 40 mg (1.2 ml) in both groups (OD group and placebo group), and it increased significantly up to 5100 mg (150 ml) in the OD group. At the end of the study 4/13 (30.7%) of the OD group were able to take the full dose of 8140 mg (245 ml) of milk: two children had a mild reaction and 2 did not have any reaction. 6/13 (46.1%) children of the OD group tolerated doses above 70 ml, but less than 150 ml; 3/13 (23%) did not tolerate doses of 70 ml, whereas all patients in the placebo group reacted at 1.2 ml. Concerning the safety of the study, the median frequency of reactions was 35% in the treated group and 1% in the placebo group: most reactions were local, 8% interested the low respiratory tract and in 4 cases epinephrine was needed.

Discussion

Up to now four RCTs on OD and two on SI are available. These studies are somewhat different because of the population enrolled (children or adults, severe allergies or mild allergies), the food causing allergy (milk, egg, peach, hazelnut) the protocol (rush, slow, rush phase followed by a slow phase), the way of SOTI administration (oral, or sublingual-swallow or sublingual-spit), and food doses administered (maximal -i.e. the regular intake-, sub-maximal -very less than the regular intake-). Moreover, put all together, these studies include only about 200 subjects. Therefore, to draw precise conclusions is rather difficult. We can say that 4 are the events that can happen after performing a SOTI program:

Table 4 - Main outcome of RCT's of oral desensitization for milk

Author	Age	Popolation	Tolerance	Partial tolerance	Non responder	Tolerance in controls
Morisset, 2007	(mean age 2.2 yr)	Less sensitive patients	24/27 (89.9%)		3/27 (11.1%)	18/30 (60%)
Longo, 2008	(mean age 7.9 yrs)	Only severe cow's milk allergy	11/30 (46%)	16/30 (54%)	3/30 (10%)	0/30 (0%)
Skripak, 2008	(mean age) 10 yrs	Excluding severe Cow's milk allergy	4/13 (30,7%) (> 250 ml)	6/13 (46,1%) (> 70 ma < 250 ml)	3/13 (23%) (< 70 ml)	0/7 (0%)

a) to reach a full tolerance, or tolerance to regular intake of the food. Most of the studies have showed that both SI and OD can accelerate the development of complete tolerance, with respect to the elimination diet. If we consider only the RCTs on cow's milk (Tab. 4), this goal seems reached at any age. Even if SOTI is more effective in the first years of life, it is probably more useful over the age of 5-6 years, when spontaneous tolerance happens more rarely. Besides, SOTI appears to be independent from the severity of cow milk allergy;

b) to reach a partial tolerance, or tolerance to lower amount of food than the regular intake. All the studies were consonant in demonstrating that both SI and OD increases the average amount of food allergen tolerated. This result should be considered important, as far as it would allow to safely intake food containing traces of allergen;

c) to reach a transient tolerance, which might disappear without a regular intake of the food. This event was first described by Rolink-Werninghouse (29) and was then confirmed by Staden. We remind that other factors, such as physical exercise, can similarly make disappear tolerance, although transiently (30);

d) to failure desensitization: SOTI must be stopped because of severe and/or repeated allergic reactions. This eventuality seems to occur only in OD studies, in about 10-20% of cases of OD for Cow's Milk Allergy.

It must be underlined that not all children successfully treated with SOTI continue to take milk over the years. Meglio (31) has reported the results obtained after a 5 years follow-up of 20 previously enrolled (17): the rate of children who still resulted tolerant to milk lowered from

85% to 70% because some children stopped taking milk after a rebound of symptoms.

With regard to safety, all studies have reported the occurrence of adverse events during SOTI, in variable percentages from 45,4% to 100%: these events are probably related to the severity of the allergies, SOTI treatment, the protocol used and the food given. Severe reactions and epinephrine administration are reported in variable percentage from 0% in SI studies, to 30,7% in OD studies, conducted both with maximal and sub-maximal protocol. Subjects unable to complete SOTI due to repeated and often severe allergic reactions vary from 0% in SI studies vs 10% to 36% OD studies (Tab. 5).

In conclusion, SOTI seems to be a possible approach to accelerate tolerance development in children affected from food allergy. However, other studies are needed to clarify which is the best treatment and protocol to follow in order to reduce the adverse events and to increase the percentage of success, before thinking that SOTI might be part of the clinical practice.

It must be stressed that in most of the studies the initial phase have been performed in hospital and that all treatment protocols have been performed in highly supervised research settings. Mortality rate for food anaphylaxis is a relatively rare event, which is estimated approximately in 1/154 (32) - 1/675 (33) episodes, and which seems to occur even if appropriate therapy has been performed. Therefore, given that so far - also considering the open studies- only few hundreds of children have been treated with SOTI, we agree with the recommendation of limiting the spread of such therapy, limitating it to selected allergologic centres (34).

Table 5 – Adverse effect and failure of RCT studies

Author	Treatment	Protocol	Adverse effect (%)	Systemic reactions	IM epinephrine administration	Unable to complete OD protocol
Enrique, 2005	Sublingual Immunotherapy (Sublingual/split)	Rush phase followed by slow phase	45,4	0.2% (3 reactions/1466 doses)	0	0% (20 g of hazelnut)
Fernandez Rivas 2009	Sublingual Immunotherapy	Rush phase followed by slow phase	100	16 systemic reactions in 5/37 (13.5%) patients	0	0 (0%)
Morrisset, 2007	Oral desensitization	Slow	?	0 (0%)	NS	3/27 (11,1%)
Staden U, 2007	Oral desensitization	Slow	100	4/25 (16%) of children had moderate side effect	0	9/25 (36%)
Longo, 2008	Oral desensitization	Rush phase followed by slow phase	100	NS	5	3 (10%) (16.6%)
Skripak, 2008	Oral desensitization (sub-maximal)	Slow	35% (median frequency for total reactions in each participant)	17,7 (Median frequency of 1% of 177 doses per participant administered)	4/13 (30.7%)	0 (0%)

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