



Oral immunotherapy for cow's milk allergy

Giovanni Passalacqua^a, Massimo Landi^b, and Giovanni B. Pajno^c

Purpose of review

Cow's milk allergy (CMA) is common in children and may lead to severe systemic reactions. Avoidance of the ingestion of cow milk is the only effective approach, but this does not exclude the inadvertent or accidental ingestion, or the assumption of milk hidden in other foods. As no pharmacological treatment is available, specific desensitization has been considered an attractive strategy.

Recent findings

In the last years, several trials of oral desensitization to cow milk, with different protocols, were published. Overall the results were favourable and demonstrated the achievement of a full tolerance in a high percentage of children. Mild side effects that can be easily managed by slowing the desensitization were reported frequently. The discontinuation of the procedure was necessary in less than 20% of children, on average, due to severe side effects.

Summary

Oral immunotherapy (oral desensitization) seems to be a promising treatment strategy for cow milk allergy in children that can be applied also to other foods such as eggs or peanuts.

Keywords

cow's milk allergy, immunotherapy, tolerance

INTRODUCTION

Cow's milk allergy (CMA) is the most common food allergy [immunoglobulin (Ig)E-mediated] in infants and young children, affecting, when objectively diagnosed, 1–3% of the general population [1–4]. Allergic reactions to cow's milk proteins can range from immediate, potentially life-threatening reactions to chronic or long-lasting diseases, thus seriously impacting the quality of life of patients and of their parents. The underlying mechanism of CMA allergy is generally IgE-mediated, and IgE can be directed towards one or more components of milk, including caseins (Bos d 8), alpha lactalbumin (Bos d 4), beta-lactoglobulin (Bos d 5) and bovine serum albumin (Bos d 6) [5,6]. The IgE mediated reactions to cow's milk usually occurs within 2 h of exposure, causing a variety of manifestations involving skin, respiratory, gastrointestinal, or cardiovascular systems. In another subset of cases the adverse reactions are cell-mediated or sustained by both IgE and nonIgE mechanisms. Cell-mediated reactions to cow's milk include food proteins induced enterocolitis syndrome (FPIES) and proctocolitis. Atopic dermatitis and eosinophilic gastrointestinal disorders are triggered by a combination of IgE and cell-mediated processes [7].

Several studies have shown that the prognosis of CMA is favourable, as the majority of patients seem to outgrow their allergy by age 3 years [1–3]. Nonetheless, retrospective reports indicated that a longer time is needed to outgrow milk allergy and that, on average, tolerance develops in adolescence rather than in early school age as previously thought [8,9]. In addition, infants without detectable specific IgE levels to cow's milk have a higher spontaneous recovery rate than those with IgE-mediated CMA [9–11].

Avoidance of CM and derivatives is still considered the first choice approach in the management of CMA in all children, wherein formulas or other mammalian milks can be used [12^{••}]. Apart from the nutritional aspects, this approach does not

^aAllergy and Respiratory Diseases, DIMI, University of Genoa, ^bPediatric National Healthcare System, Turin and ^cDepartment of Pediatrics, Allergy Unit, University of Messina, Messina, Italy

Correspondence to Giovanni Passalacqua, MD, Allergy and Respiratory Diseases, University of Genoa, Pad. Maragliano, L.go R. Benzi 10, 16132 Genoa, Italy. Tel: +39 01 0353 8933; fax: +39 01 0353 8904; e-mail: passalacqua@unige.it

Curr Opin Allergy Clin Immunol 2012, 12:000–000

DOI:10.1097/ACI.0b013e3283535b93

KEY POINTS

- Cow's milk allergy is frequent in children and the only effective treatment is avoidance of the food, but rarely this can be complete. Thus, the induction of tolerance by giving gradually increasing amounts of milk is an attractive approach.
- Independently of the protocol used, a full tolerance to milk can be achieved in about 80% of children, with only mild side effects.
- What still needs to be clarified is whether the induced tolerance is permanent or transient and which mechanisms are involved. Investigations on those aspects would allow making cow milk immunotherapy even more effective and safe.

exclude the risk of the accidental ingestion of milk, or of the unaware ingestion of foods containing milk or milk-derivatives. In addition, the indications on how long milk should be avoided before its re-introduction in diet are variable [12²²,13,14], and usually children should be reassessed each year to ascertain whether their allergy has been outgrown.

On the other hand, no effective pharmacological treatment is available to cure (or to provide long-term remission from) CMA. Thus, a safe, cheap and affordable therapeutic approach would be needed, to be offered at least to patients who are at risk of severe adverse reactions. In this sense, allergen-specific immunotherapy (SIT), or allergen desensitization, is capable of modifying the IgE-mediated immune response and of achieving a long-term protection, as happens in respiratory or hymenoptera venom allergy [15²³]. For this reason, the immunotherapy approach was regarded as an attractive strategy to treat food allergy starting from the early 1980s, but the first attempts made with subcutaneous peanut extracts led to an unacceptable rate of severe adverse events [16,17]. Thus, the oral administration of foods to achieve a tolerance or desensitization was proposed, and this seemed to be particularly suitable for CMA. Several clinical studies on the argument are available and other trials are currently under way to better define indications, contraindications and practical aspects. Of note, there is no specific study for non IgE-mediated food allergy.

IMMUNOTHERAPY OR TOLERANCE INDUCTION?

In a strict sense, allergen immunotherapy describes the administration of gradually increasing doses of

the allergen that reduces symptoms due to natural allergen exposure, induces measurable immunological changes (e.g. IgE, IgG4, Th1/Th2 balance, T regulatory cells) and possibly maintains the tolerant status with periodical delayed administrations of the offending allergens [18]. According to this, in the case of CMA a 'permanent' tolerance should be expected, which implies that the food can be ingested without the appearance of allergic symptoms despite periods of withdrawal. On the contrary, tolerance induction is generally intended as the administration of the offending substance, until a 'natural occurring dose' is tolerated. This is commonly done with aspirin or other drugs [19]. In the latter case, usually the patient has to regularly and continuously assume the substance to maintain the tolerant status, as when ingestion is interrupted or discontinued, the protective effect may be lost or significantly decreased. In the case of CMA, there are not sufficient data to ascribe the desensitization procedures to one or the other type of approach. [20,21,22²⁴]. In fact, in the available literature (see below), although usually patients have ascertained IgE-mediated CMA, the immunological changes were investigated less in depth than for aeroallergen immunotherapy, the induction protocols were largely variable, and long-term data are few. Moreover, it is still unclear whether oral desensitization is only the first step toward permanent desensitization or it induces only a transient tolerance [20]. On the other hand, in westernized countries and in real life, the continuous or frequent ingestion of foods, such as cow's milk or hen's egg, after the achievement of desensitization is *per se* easy to do by patients. Therefore, active specific therapy could be successful for some food allergens, even without the induction of a true permanent tolerance.

As to the question of whether the oral/sublingual treatment of CMA is a true specific immunotherapy, or a tolerance induction is still unresolved, we will use subsequently the conventional term of oral immunotherapy (OIT) to designate all those approaches that imply the administration of increasing doses of cow's milk via enteric routes to achieve a symptom reduction.

ORAL IMMUNOTHERAPY FOR CMA: THE LITERATURE

Apart from the very early and pioneeristic attempts, mainly described as case reports [23–26], the literature concerning OIT for CMA is currently not negligible, although the quality of the clinical trials is far from being optimal (see Table 1) [27–35, 36,37²⁵,38,39²⁶]. One of the first controlled trials (although open and not randomized) [27] reported

Table 1. Clinical trials of oral desensitization for Cow milk allergy

Author (reference)	Design	Number of patients	Age range	Duration of induction	Main results
Patriarca <i>et al.</i> [27]	Open controlled nonrandomized	6 OIT 10 avoidance	3–14	12 months	Tolerance obtained in all patients.
Patriarca <i>et al.</i> [28]	Open controlled, nonrandomized	29 OIT 16 no treatment	13 adult 16 child	4 months	5 dropout; 5 discontinued for severe side effects. 19 patients achieved tolerance. Significant increase in IgG4.
Meglio <i>et al.</i> [29]	Prospective not controlled	21	6–10	6 months	15/21 full tolerance; 3/21 partial tolerance; 3 discontinued for side effects. No change in specific IgE.
Staden <i>et al.</i> [30]	Randomized open controlled	14 OIT 10 avoidance	1–13	67 days	Results not reported separately for cow's milk and egg. Overall 48% tolerant, 16% partly tolerant; 16% failure.
Martorell <i>et al.</i> [31]	Prospective not controlled	4	2–5	5 days	Full tolerance in all patients (200 ml), maintained at 3 years. Decrease in IgE and cutaneous reaction.
Morrisset <i>et al.</i> [33]	Randomized, open, controlled	30 OIT 27 avoidance	1.5–6.5	6 months	SBPCFC positive after 6 months in 11% of OIT patients and 50% of avoidance patients.
Staden <i>et al.</i> [32]	Prospective not controlled	9	3–10	3–7 days	6/9 full tolerance (120 ml); 3/9 partial tolerance limited by side effects.
Longo <i>et al.</i> [34]	Randomized, open, controlled	30 OIT 30 avoidance	5–17	10 days (hospital) + 3 months (home)	11/30 full tolerance (150 ml); 16/30 partial tolerance (5–150 ml); 3 discontinued for persistent side effects. Significant difference between groups at the DBPCFC.
Skripak <i>et al.</i> [35]	Randomized, DBPC	13 OIT 7 placebo	6–21	23 weeks	Significant increase in the threshold dose of cow's milk protein (40 vs. 8,140 mg) after OIT. No change in placebo group. Increase in IgG4.
Zapatero <i>et al.</i> [36]	Prospective	18	4–8	10–32 weeks	16/18 full tolerance (200 ml); 1 /18 partial tolerance; 1 dropout. Decrease cutaneous reaction.
Pajno <i>et al.</i> [37 ^{***}]	Randomized, SB controlled	15 OIT 15 soy milk	4–10	18 weeks	2/15 dropout; 2/13 failed for side effects; 1/15 partial tolerance; 10/15 full tolerance. Significant increase in IgG4.
Kaneko <i>et al.</i> [38]	Prospective not controlled	10	4–14	200 days	8/10 full tolerance (250 ml), 2 stopped due to side effects.
Martorell <i>et al.</i> [39 [■]]	Randomized, open controlled	30 OIT 30 avoidance	2–3	1 year	Full tolerance in 90% OIT patients vs. 23% in controls. Significant decrease IgE.

DBPCFC, double blind placebo controlled food challenge; DBPC, double blind placebo controlled; OIT, oral immunotherapy; SDBPCFC, single double blind placebo controlled food challenge.

a successful tolerance to milk in all the six patients enrolled. The same researchers [28], using OIT protocols for various foods, induced an effective desensitization in 75% of participants. The most common food allergy was milk, followed by egg and fish. In comparison with age-matched food allergic controls, individuals receiving OIT experienced a significant decrease in food-specific IgE and an increase in specific IgG4.

Meglio *et al.* [29] with a 6-month OIT protocol successfully desensitized 15/21 children with proven IgE-mediated CMA, and partially desensitized three children. Staden *et al.* [30] compared oral desensitization and elimination diet in 47 children allergic to cow's milk (34 patients) or hen's egg. The patients were randomly assigned to OIT or elimination diet as a control group. Re-evaluation of clinically relevant food allergy was performed by food challenge after a median of 21 months. Interestingly, after OIT, children were placed on elimination diet for 2 months before repeating the double-blinded placebo-controlled food challenge (DBPCFC) in order to evaluate any persistence of the induced tolerance. An equal percentage (35%) of children in both active and control groups displayed tolerance at the DBPCFC, but also 'partial responders' to OIT were described, and the global (total + partial tolerance) rate of responses was 64% in the active group. The patients who achieved full tolerance were able to discontinue the intake of the culprit foods without further appearance of allergic symptoms. Two small prospective trials [31,32] reported a successful tolerance induction using a very short protocol (3–5 days), with a relatively small proportion of side effects, but those studies were limited to 13 patients only and without any control. Morisset *et al.* [33] studied in a randomized open fashion a total of 57 children and found a significant increase in the food challenge (single blind) in a significantly higher proportion of OIT patients. Longo *et al.* [34] studied 60 children, 5 years of age or older with a history of severe allergic reactions to milk ingestion. Approximately 80% of participants in this study had milk-specific IgE levels greater than 100 kU/l with a mean skin prick test wheal size of 11–12 mm. One half received immunotherapy for 1 year, and the second half were observed with conventional elimination diet. The OIT was carried out for 10 days in the hospital and continued until a dose of 20 ml of pure cow's milk was reached. In the OIT group, 36% were able to tolerate a single feeding of 150 ml, 54% could ingest 5–50 ml and 10% interrupted the study because of serious unwanted effects. Conversely, most children in the observation group had no change in their milk reaction threshold, and none was able to

tolerate 5 ml. Almost all children in the OIT group experienced allergic symptoms during the protocol, mainly urticaria and angioedema.

In the first randomized DBPC trial of OIT, 20 children with IgE-mediated CMA were randomized to milk or placebo OIT [35]. The desensitization involved three phases: 1 day of build-up in-office (initial dose 0.4 mg of milk protein, final dose 50 mg), a 8-week in-office dose increase to a maximum of 500 mg and, finally a daily maintenance dose at home for 3–4 months. Nineteen patients, 6–17 years of age, completed the treatment, 12 in the active group and seven in the placebo group. The median milk threshold dose in both groups was 40 mg at the baseline DBPCFC. After OIT, the median threshold dose in the active treatment group was 5240 mg (range 2540–8140), whereas all patients in the placebo group only tolerated 40 mg ($P=0.0003$). All children in the active treatment group experienced mild to moderate adverse reactions. Milk-specific IgE did not change significantly in the active group, whereas IgG4 increased significantly. The patients previously on placebo were then switched to OIT, and showed at the follow-up the acquisition of tolerance to cow's milk [40]. Results similar to those of previous trials were also reported by Zapatero *et al.* [36] in 18 children, of which 16 achieved a full tolerance. Pajno *et al.* [37] evaluated the safety and efficacy of OIT with a modified protocol, using a single blind design with soy milk as control. The protocol involved weekly outpatient-increasing dose comprising 28 visits over 4 months. Thirty children with confirmed CMA via DBPCFC were randomized to receive active therapy or soy milk. The primary outcome was the reduction in clinical sensitivity, as demonstrated by a change in threshold dose via DBPCFC. The secondary outcome was the immunologic changes. OIT was effective, with 10 of 13 individuals tolerating 200 ml cow's milk, and one with partial tolerance. Two children had to stop the OIT because of severe reactions. No change was seen in specific IgE levels, as in other trials [29,33,38] but in the actively treated group, there was a significant increase in specific IgG4. Recently, an interesting case-control study [39] showed a high rate of desensitization (90%) in patients suffering from CMA. However, this trial was carried out in toddlers aged 2 years without waiting for the spontaneous resolution of symptoms that is quite common before the age of 4 or 8 years. Finally, there is also an uncontrolled pilot study of sublingual immunotherapy (SLIT), performed in eight children with CMA [41]. Milk was kept in the mouth for 2 min and then spat out. Seven children completed the protocol, and one child withdrew because of persistent oral symptoms.

Table 2. Side effects in the published oral immunotherapy studies

Author (Reference)	Number of patients	OIT discontinued for side effects	Total occurrence of side effects
Patriarca <i>et al.</i> [27]	6 OIT 10 avoidance	None	None reported
Patriarca <i>et al.</i> [28]	29 OIT 16 no treatment	5/29 (17%)	51%
Meglio <i>et al.</i> [29]	21 OIT	3/21 (14%)	62%
Staden <i>et al.</i> [30]	14 OIT 10 avoidance	9/25 (overall, not specified for cow's milk separately)	100%
Martorell <i>et al.</i> [31]	4 OIT	0/4	100%
Morrisset <i>et al.</i> [33]	30 OIT 27 avoidance	3/30 (10%)	Not specified
Staden <i>et al.</i> [32]	9 OIT	1/9 (11%)	100%
Longo <i>et al.</i> [34]	30 OIT 30 avoidance	3/30 (10%)	100%
Skripak <i>et al.</i> [35]	13 OIT 7 placebo	0/13	47%
Zapatero <i>et al.</i> [36]	18 OIT	2/18 (11%)	68%
Pajno <i>et al.</i> [37 [■]]	15 OIT 15 soy milk	2/13 (15%)	77%
Kaneko <i>et al.</i> [38]	10	2/10 (20%)	Not described
Martorell <i>et al.</i> [39 [■]]	30 OIT 30 avoidance	1/30 (3%)	80% (47% moderate, 33% mild)

OIT, oral immunotherapy.

After 6 months of treatment, the threshold dose of milk increased from a mean of 39 ml to 143 ml ($P < 0.01$).

SAFETY OF MILK ORAL IMMUNOTHERAPY

The appearance of adverse reactions during OIT for CMA is reported frequently. In most studies 100% of patients experienced adverse reactions during desensitization (Table 2) [30–35,36,37[■],38,39[■]], but OIT had to be discontinued in less than 20% of subjects. Severe systemic side effects have been reported independently of the schedule, that is either with rush [31,32], weekly [37[■]], or slow up dosing regimens [35,38]. The frequency of serious events and the severity of reactions are greater during the initial phase and tend to decrease in intensity as the desensitization proceeds and higher doses of cow's milk are administered. Mild reactions such as abdominal pain, throat pruritus, gritty eyes, watery eyes, transient erythema and sneezing usually do not require stopping desensitization. On the contrary, when rhinitis, dyspnoea, asthma, generalized urticaria and hypotension occur, as a single symptom or in combination, OIT should be postponed or, better, stopped. A life-threatening asthma reaction caused by desensitization to milk was described by Nieto *et al.* [42]. Adverse events are largely unpredictable, and they can occur during home dosing, and systemic reactions have occurred with previously tolerated doses in the occasion of exercise [43], viral illness or sub-optimally controlled asthma [29]. Of note, these reactions are usually well controlled by antihistamines, steroids

or epinephrine. Because desensitization(s) place patients at risk for systemic reactions, it is not appropriate to implement OIT in clinical practice settings at this time. Therefore, OIT can be performed for research purposes for IgE-mediated food allergy in specialized pediatric centers.

CONCLUSION

CMA represents a promising field of application for SIT, especially in its oral (or sublingual) form [44,45]. The published studies, allowed to perform a meta-analysis, which confirmed the overall benefit of the treatment, although not all the studies provided consistent results [46[■]]. However, there are numerous unresolved questions and many aspects need to be elucidated before recommendations can be made. On one hand, the procedure is time-consuming and not devoid of side effects, whereas we know that many children with CMA develop tolerance spontaneously, and can be easily managed with the simple avoidance regimen. Therefore, waiting until at least the age of 3 years before starting OIT seems to be a reasonable choice. On the contrary, the avoidance regimen may be insufficient in children with severe systemic reactions, because of the risk of inadvertent cow's milk intake or of the assumption of foods containing milk as hidden allergen. In such patients, an effective tolerance induction would represent a life-saving treatment. Thus, more clear indications on the eligible patients and the predictive factors are urgently needed. Another aspect that must be clarified is if the tolerant status achieved by OIT is permanent or if it needs to be maintained indefinitely with a regular milk

intake. This aspect is strictly dependent on the knowledge of the mechanisms of action of OIT, on which there are very few data. Finally, the proposed OIT regimens are largely variable and not standardized, thus making it difficult to compare the results of the different studies.

OIT represents an emerging reality that provides both hope and optimism for patients with CMA and expands the possibility of an active treatment with the goal of improving the quality of life for children and their families. This is reinforced by the recent encouraging results obtained with other forms of desensitization, such as the SLIT [47^{***}] and the epicutaneous ones [48]. At the present time, OIT cannot be recommended as a routine practice, but must be limited to a research setting, and performed only by trained physicians and under strict medical supervision [12^{***}].

Acknowledgements

None.

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

1. Saarinen KM, Juntunen-Backman K, Jarvenpää AL, *et al.* Supplementary feeding in maternity hospitals and the risk of cow's milk allergy: a prospective study of 6209 infants. *J Allergy Clin Immunol* 1999; 104:457–461.
2. Steinke M, Fioocchi A, Kirchlechner V, *et al.* Food allergy in children and potential allergy medicine users in Europe: a randomised telephone survey of children in 10 European nations. *Int Arch Allergy Immunol* 2007; 143:290–295.
3. Fioocchi A, Terracciano L, Bouygue GR, *et al.* Incremental prognostic factors associated with cow's milk allergy outcomes in infant and child referrals: the Milan Cow's Milk Allergy Cohort study. *Ann Allergy Asthma Immunol* 2008; 101:166–173.
4. Venter C, Pereira B, Grundy J, *et al.* Incidence of Parentally reported and clinically diagnosed food hypersensitivity in the first year of life. *J Allergy Clin Immunol* 2006; 117:1118–1124.
5. Wal J-M. Cow's milk proteins/allergens. *Ann Allergy Asthma Clin Immunol* 2002; 89 (Suppl 9):3–10.
6. Restani P, Ballabio C, Di Lorenzo C, *et al.* Molecular aspects of milk allergens and their role in clinical EVENTS Anal Bioanal Chem 2009; 395:47–56.
7. Boyce JA, Assa'ad A, Burks AW, *et al.* Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. *J Allergy Clin Immunol* 2010; 126 (6 Suppl):S1–S58.
8. Niggemann B, Staden U, Rolinck-Werninghaus C, Beyer K. Specific oral tolerance induction in food allergy. *Allergy* 2006; 61:808–811.
9. Saarinen KM, Peltkonen AS, Mäkelä MJ, Savilahti E. Clinical course and prognosis of cow's milk allergy are dependent on milk-specific IgE status. *J Allergy Clin Immunol* 2005; 116:869–875.
10. Sicherer SH, Sampson SH. Food allergy. *J Allergy Clin Immunol* 2010; 125 (Suppl 2):S116–S125.
11. Skripak JM, Matsui EC, Mudd K, Wood RA. The natural history of IgE-mediated cow's milk allergy. *J Allergy Clin Immunol* 2007; 120:1172–1177.
12. Fioocchi A, Brozek J, Schünemann H, *et al.* World Allergy Organization (WAO) ■ special committee on food allergy. World Allergy Organization (WAO) Diagnosis and Rationale for Action against Cow's Milk Allergy (DRACMA) guidelines. *Pediatr Allergy Immunol* 2010; 21 (Suppl 21):1–125.
13. Muraro A. Dietary prevention of allergic diseases in infants and small children. Part II. evaluation of methods in allergy prevention studies and sensitization markers. Definitions and diagnostic criteria of allergic diseases. *Pediatr Allergy Immunol* 2004; 15:196–205.
14. Prescott SL. The Australasian society of clinical immunology and allergy position statement: summary of allergy prevention in children. *Med J Aust* 2005; 182:464–467.
15. Shamji MH, Durham SR. Mechanisms of immunotherapy to aeroallergens. ■ *Clin Exp Allergy* 2011; 41:1235–1246.
16. Oppenheimer JJ, Nelson HS, Bock SA, *et al.* Treatment of peanut allergy with rush immunotherapy. *J Allergy Clin Immunol* 1992; 90:256–262.
17. Nelson HS, Lahr J, Rule R, *et al.* Treatment of anaphylactic sensitivity to peanuts by immunotherapy with injections of aqueous peanut extract. *J Allergy Clin Immunol* 1997; 99 (6 Pt 1):744–751.
18. Bousquet J, Lockey R, Malling HJ. Allergen immunotherapy: therapeutic vaccines for allergic diseases. A WHO position paper. *J Allergy Clin Immunol* 1998; 102 (4 Pt 1):558–562.
19. Klimek L, Pfaff O. Aspirin intolerance: does desensitization alter the course of the disease? *Immunol Allergy Clin North Am* 2009; 29:669–675.
20. Scurlock AM, Burks AW, Jones SM. Oral Immunotherapy for food allergy. *Curr Allergy Asthma Rep* 2009; 9:186–193.
21. Rolinck-Werninghaus C, Staden U, Mehl A, *et al.* Specific oral tolerance induction with food in children: transient or persistent effect on food allergy? *Allergy* 2005; 60:1320–1322.
22. Vickery BP, Scurlock AM, Jones SM, Burks WA. Mechanisms of immune ■ tolerance relevant to food allergy. *J Allergy Clin Immunol* 2011; 127:576–584.
23. Vaillaud JC, Manasser J, Poiree M. Intolerance a la betalactoglobuline avec choc anaphylactique, améliorée par la desensibilisation. *Pédiatrie* 1969; 24:585–595.
24. Poisson A, Thomas G, Jean-Landais N, Giaufre E. Rapid habituation of oral cow's milk allergy in one case with severe ailment at birth [in French]. *Rev Fr Allergol* 1987; 27:31–32.
25. Patriarca G, Romano A, Venuti A, *et al.* Oral specific hyposensitization in the management of patients allergic to food. *Allergol Immunopathol* 1984; 12:275–281.
26. Bauer A, Ekanayake Mudiyanse S, Wigger-Alberti W, Elsner P. Oral rush desensitization to milk. *Allergy* 1999; 54:894–895.
27. Patriarca G, Schiavino D, Nucera E, *et al.* Food allergy in children: results of a standardized protocol for oral desensitization. *Hepato-Gastroenterol* 1998; 45:52–58.
28. Patriarca G, Nucera E, Roncallo C, *et al.* Oral desensitizing treatment in food allergy: clinical and immunological results. *Aliment Pharmacol Ther* 2003; 17:459–465.
29. Meglio P, Bartone E, Plantamura M, *et al.* A protocol for oral desensitization in children with IgE-mediated cow's milk allergy. *Allergy* 2004; 59:980–987.
30. Staden U, Rolinck-Werninghaus C, Bewe F, *et al.* Specific oral tolerance induction in food allergy in children: efficacy and clinical patterns of reaction. *Allergy* 2007; 62:1261–1269.
31. Martorell Aragonés A, Félix Toledo R, Cerdá Mir JC, Martorell Calatayud A. Oral rush desensitization to cow milk. Following of desensitized patients during three years. *Allergol et Immunopathol* 2007; 35:174–176.
32. Staden U, Blumchen K, Blankenstein N, *et al.* Rush oral immunotherapy in children with persistent cow's milk allergy. *J Allergy Clin Immunol* 2008; 122:418–419.
33. Morisset M, Moneret-Vautrin DA, Guenard L, *et al.* 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. *Eur Ann Allergy Clin Immunol* 2007; 39:12–19.
34. Longo G, Barbi E, Berti I, *et al.* Specific oral tolerance induction in children with very severe cow's milk-induced reactions. *J Allergy Clin Immunol* 2008; 121:343–347.
35. Skripak JM, Nash SD, Rowley H, *et al.* A randomized, double blind, placebo controlled study of milk oral immunotherapy for cow's milk allergy. *J Allergy Clin Immunol* 2008; 122:1154–1160.
36. Zapatero L, Alonso E, Fuentes V, Martínez MI. Oral desensitization in children with cow's milk allergy. *J Investig Allergol Clin Immunol* 2008; 18:389–396.
37. Pajno GB, Caminiti L, Ruggeri P, *et al.* Oral immunotherapy for cow's milk ■ allergy with a weekly up-dosing regimen: a randomized single-blind controlled study. *Ann Allergy Asthma Immunol* 2010; 105:376–381.
38. Kaneko H, Teramoto T, Kondo M, *et al.* Efficacy of the slow dose-up method for specific oral tolerance induction in children with cow's milk allergy: comparison with reported protocols. *J Investig Allergol Clin Immunol* 2010; 20:538–539.
39. Martorell A, De la Hoz B, Ibanez MD, *et al.* Oral desensitization as a useful ■ treatment in 2-year-old children with cow's milk allergy. *Clin Exp Allergy* 2011; 41:1297–1304.

The more recent study on oral desensitisation carried out in toddlers, thus investigating a special population for which OIT is expected to represent a valuable option.

40. Narisety SD, Skripak JM, Steele P, *et al.* Open-label maintenance after milk oral immunotherapy for IgE-mediated cow's milk allergy. *J Allergy Clin Immunol* 2009; 124:610–612.
41. De Boissieu D, Dupont C. Sublingual immunotherapy for cow's milk protein allergy: a preliminary report. *Allergy* 2006; 61:1238–1239.
42. Nieto A, Fernandez-Silveira L, Mazon A, Caballero L. Life-threatening asthma reaction caused by desensitization to milk. *Allergy* 2010; 65: 1342–1343.
43. Caminiti L, Passalacqua G, Vita D, *et al.* Food-exercise-induced anaphylaxis in a boy successfully desensitized to cow milk. *Allergy* 2007; 62:335–336.
44. Nowak-Węgrzyn A, Fiocchi A. Is oral immunotherapy the cure for food allergies? *Curr Opin Allergy Clin Immunol* 2010; 10:214–219.
45. Nowak-Węgrzyn A, Sampson HA. Future therapies for food allergies. *J Allergy Clin Immunol* 2011; 127:558–573.
46. Brożek JL, Terracciano L, Hsu J, *et al.* Oral immunotherapy for IgE-mediated cow's milk allergy: a systematic review and metaanalysis. *Clin Exp Allergy* 2012; 42:363–374.
 ■■ This is the first systematic meta-analysis on OIT in cow's milk allergy. It showed a significant benefit effect and a significantly increased likelihood of achieving full tolerance.
47. Kim EH, Bird JA, Kulis M, *et al.* Sublingual immunotherapy for peanut allergy: clinical and immunologic evidence of desensitization. *J Allergy Clin Immunol* 2011; 127:640–646.
 ■■ An elegant controlled trial demonstrating the clinical and immunological effects of sublingual immunotherapy in IgE-mediated peanut allergy.
48. Dupont C, Kalach N, Soulaines P, *et al.* Cow's milk epicutaneous immunotherapy in children: a pilot trial of safety, acceptability, and impact on allergic reactivity. *J Allergy Clin Immunol* 2010; 125:1165–1167.