

# Oral desensitization for milk allergy in children: state of the art

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### Purpose of review

The purpose of this review is to research current evidence on cow's milk oral immunotherapy for the treatment of cow's milk allergy (CMA).

### Recent findings

The specific, active treatment for IgE-mediated food allergy included CMA, which is currently being investigated in human trials. Allergen-specific approaches include oral, sublingual and epicutaneous immunotherapy. Reports on oral immunotherapy (OIT) for the treatment of milk allergy have been more extensive and carried out mostly with native proteins. The aim of OIT with cow's milk is the achievement of desensitization or tolerance by patients suffering from CMA. Desensitization state can be achieved by approximately 36–92% of the children treated with specific immunotherapy; the rate of permanent tolerance is unknown. Longer duration of desensitization may result in permanent tolerance. The possibility of adverse events or reactions during OIT is quite frequent. Side-effects have been reported by patients in all published studies.

### Summary

OIT as an active treatment for CMA represents an emerging reality. Before this treatment can be used in clinical practice, additional studies are needed. Currently, many issues remain unanswered: severity and type of food allergy responsive to specific immunotherapy, degree of protection, 'shared schedules' of desensitization(s) in research settings and well established risk-to-benefit ratio. However the field of specific, active treatment of food allergy is poised for clinically important advances.

### Keywords

cow's milk allergy, desensitization, oral immunotherapy, tolerance

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## Introduction

The adverse immune reactions to cow's milk proteins can range from immediate, potentially life-threatening reactions to chronic disorders. Cow's milk allergy (CMA) is the most common food allergy in infants and young children, affecting 2–3% of general population [1–4]. Most studies have shown the prognosis for developing tolerance to cow's milk to be good, with the majority outgrowing their allergy by age 3 years [1–4].

It has been shown that infants with CMA, but without detectable specific IgE levels to cow's milk, have a higher spontaneous recovery rate compared with infants with high levels of specific IgE toward milk proteins, that is, IgE-mediated CMA [5–7]. However recent reports indicate that children need longer to outgrow their milk allergy, with most developing tolerance in their teenage years rather than in early school as previously thought [6,8].

Because no treatments are available to cure or provide long-term remission from food allergy, allergen-specific

treatments and strategies that attempt to alter the allergic response to specific food allergens are expected. The approach that attracts a significant interest in the scientific community, as well as the public and media, is oral immunotherapy (OIT) [9].

A need clearly exists for 'active' therapies that allow food allergic individuals to tolerate their specific food allergens.

Recently, multiple studies have been published, and others are underway at various stages of research that focused on the practice of OIT.

OIT, sublingual (SLIT) and epicutaneous immunotherapy (EPIT) have been studied for the treatment of IgE-mediated CMA, although reports on OIT thus far have been more extensive.

## Desensitization versus (or toward) tolerance?

The goal of OIT is permanent oral tolerance, which is established when the food can be ingested without the

appearance of allergic symptoms despite periods of withdrawal. On the contrary, desensitization is marked by the necessity for the patients to regularly ingest the food allergen(s). Therefore, when ingestion is interrupted or discontinued, the protective effect of OIT may be lost or significantly decreased.

Currently, it is still unclear whether oral desensitization is the first step toward permanent oral tolerance. As with other kinds of immunotherapy (i.e. for inhalant allergens), the duration of desensitization could be pivotal for achieving tolerance (Fig. 1).

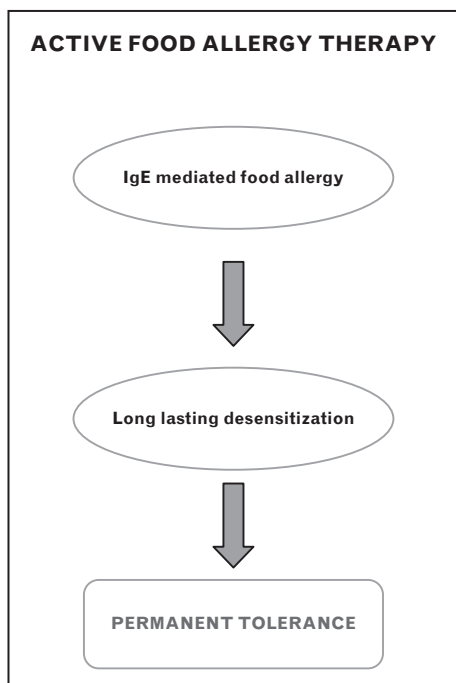
Although clinical desensitization and immune modulation have been demonstrated with OIT, the strength of the current evidence from clinical trials is insufficient concerning the induction of tolerance [10,11].

On the other hand, in the 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.

### Milk immunotherapy

An uncontrolled pilot study of SLIT was done in eight children with CMA [12]. Milk was kept in the mouth for

**Figure 1 Goal of allergen-specific oral immunotherapy for the treatment of IgE-mediated cow's milk allergy**



2 min and then spit out. Seven children completed the protocol, and one child withdrew because of continued oral symptoms. After 6 months of treatment, the threshold dose of milk increased from a mean of 39 ml at baseline to 143 ml ( $P < 0.01$ ).

In a standardized, OIT protocol for treatment of a variety of food allergies, Patriarca *et al.* [13] induced 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. Using a 6-month OIT protocol in children with proven IgE-mediated hypersensitivity to cow's milk, Meglio *et al.* [14] fully desensitized 15 of 21 children and partially desensitized three children.

Staden *et al.* [15] compared tolerance induction and elimination diet in 47 children allergic to cow's milk or hen's egg. The patients were randomly assigned to OIT or elimination diet as a control group. Re-evaluation of clinical relevant food allergy was performed by food challenge after a median of 21 months. Interestingly, children in the OIT group were placed on a secondary elimination diet for 2 months before a double-blinded placebo-controlled food challenge (DBPCFC) to evaluate the persistence of induced oral tolerance. In this study, a similar percentage (35%) in both the treatment and control group displayed tolerance by passing a challenge off therapy, although a number of 'partial responder' to OIT were seen, which increased the rate (total with partial) of response(s) to 64%.

Therefore, the patients who reached total tolerance were able to discontinue the intake of 'previous culprit foods' without the risk of further appearance of allergic symptoms.

Longo *et al.* [16] studied 60 children 5 years of age or older with histories 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 management. 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. Of those treated with OIT, 36% were able to tolerate a single feeding of 150 ml, 54% could ingest 5–50 ml and 10% (three children) interrupted the study because of serious unwanted effects. Conversely, most children in the observation group saw no change in their milk reaction threshold, and none were able to tolerate 5 ml. Almost all children in the OIT group experienced

allergic symptoms during the protocol that primarily involved urticaria and angioedema.

In the first randomized DBPC trial of OIT, 20 children with IgE-mediated milk allergy were randomized to milk or placebo OIT [17]. Dosing occurred in three phases: the build-up in-office day (initial dose 0.4 mg of milk protein, final dose 50 mg), daily dose with eight weekly in-office dose increases to a maximum of 500 mg and continued daily maintenance doses at home for 3 to 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 5 240 mg (range 2 540–8 140), 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 levels did not change significantly in the active group. Milk-specific IgG4 levels increased significantly only in the active treatment group.

In a follow-up open-label study [18], the ingestion of tolerated cow's milk was carried out at home. Adverse reactions were quite common, with several systemic reactions occurring in association with exercise or febrile illness.

Pajno *et al.* [19<sup>\*</sup>] evaluated the safety and efficacy of OIT by means of a new study protocol. This was carried out by performing a weekly outpatient increasing dose protocol comprising 28 visits over 4 months. Thirty children with

confirmed CMA via DBPCFC were randomized to receive active therapy or sham protocol with use of soy. 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 associated with this procedure. OIT was effective, with the tolerated 'full' milk dose of 200 ml in 10 of 13 individuals, partial tolerance in one, but two required discontinuation because of severe reactions associated with the OIT protocol (Table 1) [15–17,19<sup>\*</sup>].

No change was seen in specific IgE levels. However, in the actively treated group, an increase was seen in IgG4 levels to cow's milk.

Recently, an interesting case–control study [20] 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 [6].

An alternative route of allergen delivery is through an epicutaneous patch (EPIT). CMA was confirmed by an oral food challenge at baseline. Children received three 48-h applications (1 mg of skimmed milk powder or 1 mg of glucose as placebo) through a skin patch each week for 3 months. EPIT-treated children had a trend toward an increased threshold dose in the follow-up oral milk challenge. There was no change in the placebo group [21]. The most common side-effects were local pruritus and eczema at the site of EPIT application.

**Table 1 Oral food desensitization for IgE-mediated cow's milk allergy**

| Study                                      | Patients (N)                                             | Success rate                                                                                                                      | Comments                                                                                                                                                                                                             |
|--------------------------------------------|----------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Staden <i>et al.</i> [15], CM and egg      | CM 14; egg 11; control group 20; age 0.6–12.9 years      | 9/35 (36%) permanent tolerance; 3/25 (12%) tolerance with regular intake (desensitization); 4/25 (16%) achieved partial tolerance | The first randomized clinical trial of OIT. The rate of spontaneous food allergy resolution in the control group (7/29, 35%) was similar to the treatment group.                                                     |
| Longo <i>et al.</i> [16], CM               | CM 60; 30 active group; 30 control group; age 5–17 years | 11/30 (37%) tolerated 150 ml of CM; 13/30 (53%) tolerated 5–150 ml                                                                | The first study including children with previous anaphylaxis to cow's milk; 3 children 10% discontinued the study because of severe systemic reaction. 17/30 children of active group reported side-effects at home. |
| Skipak <i>et al.</i> [17], CM              | CM 20; active to placebo; ratio 2 : 1; age 6–21 years    | 12 (92%) of active group reached the dose 5140 mg of CM (range 2540–8140 mg); no change in the placebo group                      | The first double-blinded, placebo-controlled clinical trial for OIT; the median frequency of side-effect was 35% in the active group compared with 1% of the placebo group.                                          |
| Pajno <i>et al.</i> [19 <sup>*</sup> ], CM | CM 30; active to placebo; ratio 1 : 1; age 4–13 years    | 10 (76%) of active group tolerated 200 ml CM; no change in the placebo group                                                      | The first blinded trial with the weekly up-dosing regimen carried out in 18 weeks. Two children (15%) of active group discontinued the trial because of systemic reaction.                                           |

Performed in randomized controlled studies. CM, cow's milk; OIT, oral immunotherapy.

### Safety of oral immunotherapy with milk

The possibility of the appearance of adverse events or reactions during OIT is quite frequent. Side-effects have been reported by patients in all trials [12–18,19\*].

Severe systemic side-effects have been reported with either rush schedule [16] or weekly up-dosing regimen [19\*]. The frequency of serious events and the severity of reactions are greatest on the initial days and least on the days following desensitization when high doses of cow's milk intake are reached by patients.

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, dyspnea, asthma, generalized urticaria and hypotension occur as a single symptom or in combination, OIT should be postponed or stopped.

A life-threatening asthma reaction caused by desensitization to milk was described by Nieto *et al.* [22].

Adverse events are largely unpredictable, and they can occur during home dosing. Several systemic reactions have occurred at previously tolerated doses in the setting of exercise [23], viral illness and suboptimally controlled asthma [18].

Of note, these reactions had been 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 or as 'avant-garde' and modern therapy for IgE-mediated food allergy in specialized pediatric centers.

### Conclusion

Food allergies, including CMA, represent a frontier in which the application of specific immunotherapy may prove more fruitful when added to current therapeutic options. The preliminary data on OIT are encouraging. However, a large number of children with CMA develop tolerance spontaneously. Therefore, waiting at least to the age of 3 before starting OIT seems reasonable. Although the progress made toward a definitive therapy for CMA has been substantial, many issues remain unanswered. The severity and the type of food allergy responsive to specific immunotherapy, degree of protection, 'shared schedules' for the desensitization(s) in research settings and well established risk-to-benefit ratio [24,25\*\*] need to be considered.

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.

### Acknowledgements

#### Conflicts of interest

Funding and conflict of interest: none to declare.

### 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).

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A very interesting review discussing active therapies for food allergy.