Oral Desensitization for Immunoglobulin E-Mediated Milk and Egg Allergies

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ABSTRACT: Food allergy is an increasingly prevalent disease in western countries, but an effective form of therapy has not yet been found. A specific active treatment for immunoglobulin E (IgE)-mediated food allergy is currently under study in human clinical trials. Allergen-specific approaches include oral, sublingual and epicutaneous immunotherapy. Currently, reports on oral immunotherapy (OIT) have been more extensive than reports on other routes such as sublingual immunotherapy (SLIT) and epicutaneous patch. The aim of OIT using foods, especially milk and egg – the cause of most common allergies in infants and young children in Europe – is the achievement of desensitization or tolerance by patients suffering from food allergy. Treatment protocols have been initiated in highly supervised research settings with the goal of finding an active treatment against IgE-mediated food allergy. The preliminary data on OIT are encouraging, and among the plethora of novel approaches the strategies most likely to advance into clinical practice include both OIT and SLIT. It is still unclear whether oral desensitization is only the first step toward permanent desensitization or whether it induces only a transient tolerance. Longer duration of desensitization may result in permanent tolerance. The occurrence of adverse events or reactions during OIT is quite frequent and has been reported in all published studies. Therefore, before this treatment can be used in clinical practice additional studies are needed. Currently, immunotherapy for cow's milk or egg allergies is a novel approach that expands the possibility of an active treatment to improve the quality of life of patients and their families.

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Adverse reactions to cow's milk and hen's egg proteins can range from immediate potentially life-threatening reactions to chronic disorders. Cow's milk allergy is the most common food allergy in infants and young children, affecting 2%–3% of the general population. Egg allergy is the second most common food allergy in infants and young children (1%–2%) [1-5]. Most studies have shown the prognosis for developing tolerance to cow's milk to be good, with the majority of patients outgrowing their allergy by age 4 years [2-5]. The appearance of spontaneous tolerance in children with egg allergy is quite frequent, but more delayed [1]. On the other hand, recent reports indicate that children need longer to outgrow their milk allergy, with most developing tolerance in their teenage years and not in elementary school as previously thought [6-8]. It has been shown that infants with food allergy but without detectable specific immunoglobulin E levels have a higher spontaneous recovery rate compared to infants with high levels of specific IgE, i.e., IgE-mediated egg or milk allergy [6,7,9]. Because the current management of food allergy is limited to strict dietary avoidance, nutrition counselling and emergency treatment of adverse reactions [10], allergy-specific treatments and strategies that attempt to alter the allergic response to specific food allergens have been conducted. The approach attracting interest in the scientific community, as well as the public and the media, is oral immunotherapy [11]. OIT and sublingual immunotherapy for the treatment of IgE-mediated food allergy have been studied, although reports on OIT thus far have been more extensive.

SELECTION OF CANDIDATES FOR ACTIVE FOOD ALLERGY THERAPIES

Food allergies alter the quality of life of food-allergic patients and their families. Fortunately, about 80% of children allergic to foods such as cow's milk or hen's egg develop spontaneous tolerance. However, patients allergic to fish, crustaceans and shellfish may show permanent allergy throughout life without achieving any form of tolerance [10]. The adverse immune reactions to food proteins can range from immediate potentially life-threatening reactions to chronic disorders. There is a need for diagnostic tests able to distinguish subjects with transient forms of food allergy from those with persistent forms. Currently there are no diagnostic tests (e.g., serum food allergen-specific IgE antibody measurement, skin-prick tests) to reliably predict the potential for spontaneous development of oral tolerance in children with food allergy. Therefore, to verify the clinical status of children with previous well-diagnosed food allergy it is essential that a

IgE = immunoglobulin E
OIT = oral immunotherapy

double-blind placebo-controlled food challenge or an open challenge be conducted periodically. Of note, it has been shown that infants with cow's milk allergy but without detectable specific IgE levels to cow's milk have a higher spontaneous recovery rate than those with IgE-mediated cow's milk allergy [6,7,9,12,13]. Thus, in order to select patients who are suitable candidates for oral immunotherapy, several factors need to be considered, such as the natural history of IgE and non-IgE-mediated allergic disorders caused by foods, food allergen exposure in infants and toddlers, and severity and type of food allergy responsive to OIT. Of note, new specific immunotherapy approaches are currently being used for the treatment of IgE-mediated food allergy; no studies are available for non-IgE-mediated food allergy.

FOOD OIT AND SLIT

At present oral immunotherapy to cow's milk is one of the most actively investigated therapeutic approaches for food allergy [Table 1]. OIT generally involves the use of a protein powder that is mixed in a vehicle food and consumed orally. Conversely, some trials administer fresh material such as cow's milk without a vehicle, and in Europe it is quite common to use fresh, naive food/s for oral immunotherapy. In a large OIT trial [12], children with challenge-proven IgE-mediated cow's milk or egg allergy were randomly assigned to OIT (n=25) or to an elimination diet (control group, n=20). A further evaluation of clinically relevant food allergy was performed after a median of 21 months. Interestingly, children in the OIT group were placed on a secondary elimination diet for 2 months before a 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 the DBPCFC off therapy, although a number of "partial responders" were noted, which increased the rate (total plus partial) of response(s) to 64%. Therefore, the patients who reached total tolerance were able to discontinue consuming previous culprit foods without risking the occurrence of allergic symptoms. Allergen-specific IgE levels decreased significantly in children with natural tolerance during an elimination diet as well as in those treated with OIT.

Oral immunotherapy is the new treatment for IgE-mediated food allergy

In the first randomized double-blind placebo-controlled OIT trial, 20 children with IgE-mediated cow's milk allergy were randomized to milk or placebo OIT [13]. The desensitization involved three phases: 1 day of build-up in office (initial dose 0.4 mg of milk protein, final dose 50 mg), an 8 week in-office dose increase to a maximum of 500 mg, and finally a daily maintenance dose at home for 3 to 4 months. Nineteen patients, 6 to 17 years of age, completed the treatment, 12 in the active group and 7 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 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, whereas IgG4 increased significantly. In a follow-up open-label study [14], 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.

Longo et al. [15] studied 60 children 5 years of age or older with histories of severe allergic reactions to milk ingestion. The subjects' milk-specific IgE levels were higher than 85 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 followed a conventional elimination diet (observation group). In the OIT group 36% were able to tolerate a single feeding of 150 ml, 54% could ingest 5–50 ml and 10% (3 children) interrupted the study because of serious adverse effects. Conversely, most children in the observation group showed no change in their milk reaction threshold and none was able to tolerate 5 ml. Adverse reactions, including systemic reactions, were common in the actively treated group, but no child suffered life-threatening anaphylaxis.

Pajno and co-researchers [16] evaluated the safety and efficacy of oral immunotherapy by means of a new study protocol: this comprised a weekly outpatient increasing-dose regimen of

SLIT = sublingual immunotherapy

DBPCFC = double-blind placebo-controlled food challenge

Table 1. Oral food desentisization for IgE-mediated cow's milk allergy

Study	Patients	Success rate	Comments
Staden et al. [12] Cow's milk and egg	Cow's milk 14 Egg 11 Controls 20 Age 0.6–12.9 yrs	9/25 (36%) permanent tolerance. 3/25 (12%) tolerance by regular intake (desensitization). 4/25 (16%) 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 et al. [15] Cow's milk	Cow's milk 30 Control 30 Age 5–17 yrs	11/30 (37%) tolerated 150 ml of cow's milk. 13/30 (53%) tolerated 5–150 ml. 3 children (10%) discontinued the study because of severe systemic reaction	The first study to include children with previous anaphylaxis to cow's milk. 17/30 children of active group reported side effect at home
Skripak et al. [13] Cow's milk	Cow's milk 20 Active to placebo (ratio 2:1) Age 6–21 yrs	12 (92%) tolerated 5140 mg	The first double-blinded placebo-controlled clinical trial for OIT, side effects occurred in 35% in the active group and 1% in the placebo group
Pajno et al. [16] Cow's milk	Cow's milk 30 Active to placebo (ratio 1:1) Age 4–13 yrs	10 (76% tolerated 200 ml. 2 (15%) discontinued the study because of severe systemic reaction	The first blinded trial with the weekly up-dosing regiment carried out in 18 weeks. No changes occurred in the control group

Performed in randomized controlled studies

28 visits over 4 months. Thirty children with confirmed cow's milk allergy via a DBPCFC were randomized to receive active therapy or a sham protocol using soy. The primary outcome was the reduction in clinical sensitivity as demonstrated by a change in threshold dose via a DBPCFC. The secondary outcome was the immunological 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 1, but in 2 subjects the protocol was discontinued because of severe reactions associated with the protocol. 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. An uncontrolled pilot study of SLIT was performed in eight children with cow's milk allergy [17]: milk was kept in the mouth for 2 minutes and then spat out. Seven children completed the protocol but one child withdrew because of continued oral symptoms. After 6 months of treatment the threshold of milk increased from a mean of 39 ml at baseline to 143 ml ($P < 0.01$). In an early study with an OIT protocol for various foods, Patriarca and team [18] induced desensitization in 75% of participants. The most common food allergy was to milk, followed by egg and fish. As compared to age-matched food allergic controls, individuals receiving oral immunotherapy experienced a significant decrease in food-specific IgE and an increase in specific IgG4. Buchanan et al. [19] treated seven children with mild symptoms (urticaria) who were allergic to egg, and six of them tolerated significantly more egg protein than at study onset. In an open study Garcia Rodriguez and colleagues [20] evaluated OIT with egg in 23 children aged 5 or older with IgE-mediated allergy to hen's egg. The children underwent a 5 day tolerance induction with raw egg and were subsequently on a regular egg intake. During the follow-up of at least 6 months egg was well tolerated by all patients. Allergic reactions were frequent throughout the treatment but in general were mild [Table 2].

Table 2. Oral food desentisization for IgE-mediated egg allergy

Study	Patients	Success rate	Comments
Staden et al. [12] Cow's milk and egg	Cow's milk 14 Egg 11 Controls 20 Age 0.6–12.9 yrs	9/25 (36%) permanent tolerance. 3/25 (12%) tolerance by regular intake (desensitization). 4/25 (16%) 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
Patriarca et al. [18] Egg (and others foods)	Active 12 Controls 16 Age < 16 yrs	10 (83.3%) completed. 2 (16.6%) withdrawn	Specific IgE showed a significant decrease and a significant increase in all active patients
Buchanan el al. [19] Egg	Open study n=7 Age 14–84 mos	2 (28.5%) achieved persistent tolerance. 2 (28.5%) achieved partial tolerance. 3 (42.8%) stopped at first challenge	All the active patients reached a protective threshold dose against accidental introduction
Garcia Rodriguez et al. [20] Egg	Open study n=23 Age 5–17 yrs	20 (86.9%) achieved tolerance. 2 (8.6%) achieved tolerance through a slower protocol. 1 (4.3%) stopped because of severe reactions	Tolerance can be achieved within a matter of days in symptomatic allergic patients even in patients with episodes of anaphylaxis

Performed study: egg allergy

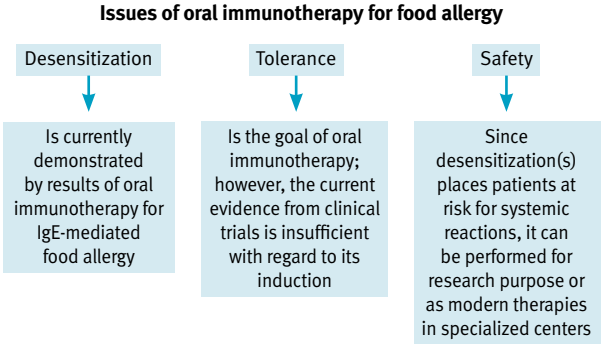
An alternative route of allergen delivery is through an epicutaneous patch. Cow's milk allergy was confirmed by an oral food challenge at baseline. Children received three 48 hour applications (1 mg skimmed milk powder or 1 mg glucose as placebo) through a skin patch each week for 3 months. Children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

THE ISSUES: DESENSITIZATION, TOLERANCE AND SAFETY

The goal of oral immunotherapy is permanent tolerance, which is established when the food can be ingested without the appearance of allergic symptoms despite periods of withdrawal. On the other hand, desensitization is marked by the ability of patients to regularly ingest the food allergen(s). Therefore, when ingestion is interrupted or discontinued, the protective effect of the oral immunotherapy may be lost or significantly decreased. Currently, it is still unclear whether oral desensitization is the first step towards permanent oral tolerance. As with other kinds of immunotherapy (e.g., for inhalant allergens), the duration of desensitization could be pivotal for achieving tolerance. Although clinical desensitization and immune modulation have been demonstrated with OIT, the strength of the evidence from clinical trials is insufficient with regard to the induction of permanent tolerance [22,23] [Figure 1].

Treatment protocols should be performed only in supervised research settings or offered as a modern advanced treatment by trained physicians

Figure 1. Oral immunotherapy is the new treatment of IgE-mediated food allergy. Despite substantial progress toward a definitive therapy for food allergy, some issues remain unanswered such as the achievement of tolerance and well-established risk-benefit ratio



The occurrence of adverse events during OIT or SLIT is quite frequent. Side effects have been reported by patients in all trials and for all routes of administration. Currently SLIT seems safer than OIT, especially when the "SLIT spit" method is used by patients [24]. The frequency of serious events and the severity of reactions are highest on the initial days and lowest on the days following desensitization when the doses of food intake are large. Mild reactions – such as abdominal pain, throat pruritus, gritty eyes, watery eyes, transient erythema, and sneezing – usually do not require stopping desensitization. On the other hand, when rhinitis, dyspnea, asthma, generalized urticaria, and hypotension occur as a single symptom or in combination, OIT should be postponed or preferably stopped.

Adverse events are largely unpredictable, and they can occur during home dosing. Several systemic reactions have occurred with previously tolerated doses in the setting of exercise [25], viral illness and suboptimal controlled asthma [14]. Of note, these reactions have been well controlled with antihistamines, steroids and epinephrine. Because desensitization places patients at risk for systemic reactions, it is not appropriate to implement OIT or SLIT in clinical practice settings at this time. Therefore, immunotherapy for food allergy should be performed for research purposes only, or as modern therapy for IgE-mediated food allergy in specialized allergy centers.

SUMMARY

Successful oral immunotherapy in a boy with egg-induced anaphylaxis was first reported in 1908 [26]. At the beginning of the 21st century this kind of treatment for food allergy was tested again in Italy by Patriarca et al. [18] and Meglio et al. [27]. At present OIT to food(s) is one of the most actively investigated therapeutic approaches for food allergy worldwide; among the plethora of novel therapies the strategies most likely to advance into clinical practice are OIT and SLIT [28]. The preliminary data on OIT and SLIT are encouraging. However, a large number of children (especially with cow's milk allergy) develop tolerance spontaneously; therefore, waiting for the child to reach at least the age of 3 before starting oral immunotherapy seems reasonable. Active treatments represent a novel approach that provides hope for patients with food allergy; with time, immunotherapy may become an efficacious and safe treatment for children with persistent symptoms caused by foods. Young patients and their families deserve better than strict allergen avoidance; therefore, the efforts of researchers in the quest to improve the care and quality of life of patients with food allergy should be encouraged.

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