

Safety profile of oral immunotherapy with cow's milk and hen egg: A 10-year experience in controlled trials

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ABSTRACT

Background: Oral immunotherapy (OIT) for food allergy is gaining interest due to the favorable clinical results reported with cow's milk, hen egg and peanut. The safety of the procedure remains a critical aspect that can limit the introduction of OIT in clinical practice.

Objective: We described herein, in detail, the occurrence and characteristics of adverse events (AE) with OIT in children who participated in controlled trials at our unit.

Methods: The clinical records of 68 children who received active treatment (40 for cow's milk and 28 for hen egg) were carefully reviewed. The inclusion and exclusion criteria, and the grading of AEs were the same across the trials. Of the 68 children involved, 6 (9%) had to discontinue the OIT procedure due to severe AEs. Fifty percent of the children underwent the buildup and maintenance phases without AEs. Mild-to-moderate AEs were documented in 28 patients, who could complete the desensitization. The majority of reactions were mild or moderate, occurred during an acute intercurrent illness and required only symptomatic treatment.

Conclusion: A careful review of the patients who received food OIT in controlled trials confirmed that AEs were not rare but that ~90% of children could achieve an effective desensitization. The procedure remains investigational and should be performed only by trained physicians, especially in the pediatric setting.

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Oral immunotherapy (OIT), also known as oral desensitization, is still considered an investigational treatment for food allergy, capable of modulating the immune response and of inducing a clinically apparent desensitization.^{1,2} OIT usually involves a slow buildup phase, with the administration of progressively increasing doses of the offending food until a tolerance to the normal dietary intake of the food itself is achieved. This phase is followed by a maintenance phase, in which the food may be regularly consumed or given on a free-diet basis. Because food allergy is typically a pediatric condition, the safety aspects of this procedure probably remains the most important aspect. The literature nowadays is abundant, and experimental trials and systematic reviews are available.^{3–6} Thus far, no fatality has been reported in the literature, but systemic reactions are consistently described as common. The rate of adverse events (AE) during OIT varies greatly in published studies,^{3,7} but mild AEs are predominant. The reporting, description,

and grading of AEs are less than ideal, and this makes it difficult to compare the real occurrence and severity of AEs among studies. This drawback also affects the identification of risk factors and their avoidance. Even the definition of anaphylaxis differs among the various guidelines.^{8,9}

Presently, the important aspects to be clarified in food OIT are the following: (a) uniformity in reporting and comparing the safety of extracts, native foods, doses, and regimens; (b) identifying those patients at risk for AEs; and (c) provision of data to physicians, patients, and their families about how to respond to a particular AE (*i.e.*, to continue, to adjust, or to stop OIT). To contribute to this aspect, we reviewed the rate and description of AEs by looking at the experience from 2006 to the present in our pediatric allergy unit, where OIT with cow's milk (CM) and hen egg (HE) were used in clinical trials. In all the trials, the specific AEs during OIT were empirically classified into mild, moderate, and severe, with appropriate actions taken, as reported in Table 1.

METHODS

The clinical records of children, ages 4–18 years, who underwent OIT for CM or HE allergy, within controlled trials, and who received an active treatment were reviewed. Our clinical records, per protocol, always reported in detail the following: demography, diagnostic procedures, prescription, discon-

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Table 1 The grading of OIT AEs used in the considered trials

	Grade 1, Mild	Grade 2, Moderate	Grade 3, Severe
OIT AE	Abdominal pain; itching of mouth, tongue, lips; throat irritation; gritty eyes; streaming and redness; erythema of the face and/or neck	Cough; sneeze and/or blockage of nose; nausea, vomiting, diarrhea, abdominal pain; swelling of lips and/or tongue; localized urticaria	Rhinitis and conjunctivitis; cough, asthma, wheezing; generalized urticaria and/or angioedema; persisting abdominal pain, nausea, vomiting, diarrhea; hypotension
Actions taken	No symptomatic treatment required; no discontinuation of OIT	Reduction of OIT doses and/or slowing up dosing; symptomatic treatment: inhaled and/or nasal antihistamines and/or corticosteroids, salbutamol, oral antihistamines	Multiple therapies required, including the following: adrenaline, systemic corticosteroids, and/or antihistamines, salbutamol, hydration, and OIT discontinuation

OIT = Oral immunotherapy; AE = adverse event.

tinuations, reasons for discontinuation, type and severity of AEs. All the patients were clearly eligible for OIT,^{3,10} based on clinical history, persistence over time of a food allergy, and confirmation of allergy by the presence of food-specific immunoglobulin E (IgE) sensitization. Double-blind, placebo-controlled food challenge was always performed, unless the clinical history was *per se* suggestive of a life-threatening reaction. OIT was administered to patients at the pediatric allergy unit of the University of Messina, after approval of the inner ethical committee and after obtaining informed consent from the parents or legal guardians.

The emergency department of the hospital was always alerted and immediately available during the procedure. OIT was administered to children by trained personnel, and on-call pediatric allergists were always available. The schedules of OIT up dosing regimens are reported elsewhere.^{2,3,10,11} Briefly, in the case of CM, the desensitization was done with increasing amounts of CM at weekly intervals, starting with 1 drop of whole CM diluted 1:25. The dose was then doubled every week until week 18, to achieve a safe intake of 200 mL. For HE, we used dehydrated egg with (DEW) obtained from eggs of *Gallus domesticus*. Also, in this case, the dose was increased on a weekly basis by using DEW diluted in sterile saline solution, starting with 0.1 mg. The dose was then doubled every week until week 16 to achieve a cumulative intake of 4 g. In all protocols, the up dosing procedures were carried out at the clinic, under medical supervision. Only the results with OIT for CM or HE were analyzed and reported.

RESULTS

Since 2006, in randomized controlled trials, 68 children with ascertained persistent IgE mediated food allergy received the OIT active treatment. OIT was performed with CM in 40 children and with HE in 28 (17 with DEW, 11 with whole HE). The median baseline IgE level was 32.7 kU/L (range, 8.8–124.6 kU/L) for CM and 36.6 kU/L (range, 5.2–110 kU/L) for HE. In the 32 patients who received the placebo OIT, no AEs were reported. Of the 68 subjects who were actively treated, 34 (50%) had AEs, and six of these subjects had to discontinue OIT; 34 patients completed the procedure per protocol without AEs; and 28 (41%) had AEs that did not lead to protocol discontinuation (Fig. 1). Thus, the overall occurrence of AEs with CM and HE desensitization was 50%.

Discontinuations Due To Severe AEs

In total, six children (9%) had to discontinue the procedure due to severe AEs. Five children (four with CM OIT and one with HE OIT) had systemic reactions (asthma, rhinitis, generalized urticaria, and hypotension) consistent with anaphylactic shock. These patients received intramuscular adrenaline, intravenous steroids, antihistamines, and inhaled salbutamol. Three of these patients had a clinical history of concomitant allergic asthma. The doses of CM that caused severe AEs were 2 mL (0.07 g) of undiluted CM in two patients, 4 mL (0.14 g) and 8 mL (0.28 g) in two other children, respectively. Another patient, during the maintenance phase, had frequent nausea and/or vomiting and/or dysphagia. An endoscopic biopsy specimen of the upper digestive tract showed a cellular infiltrate (eosinophils predominant) in the esophageal

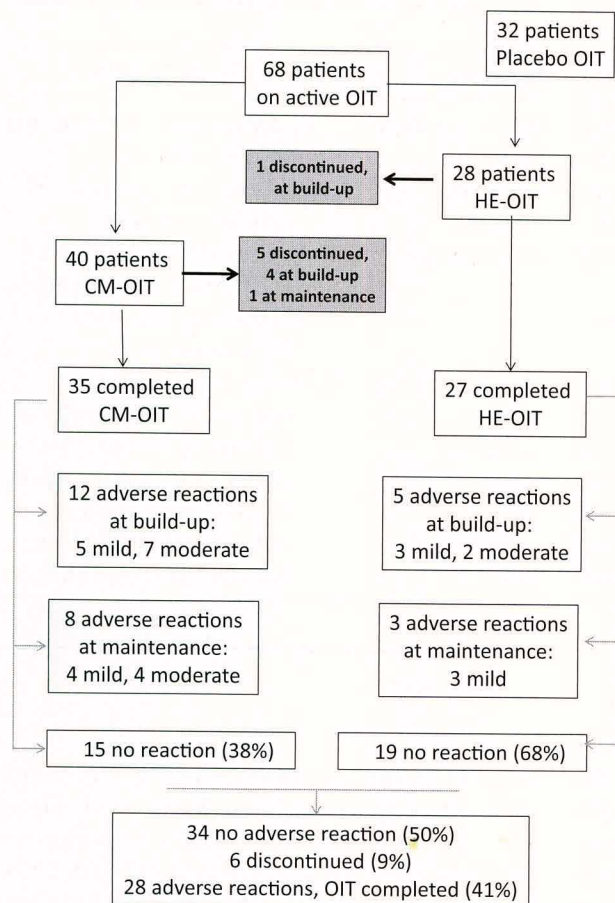


Figure 1. Disposition of the patients who received active oral immunotherapy (OIT) for hen egg (HE) or cow's milk (CM).

epithelium, with intercellular edema and basal zone hyperplasia. Also in this case, OIT was stopped. The patients who were CM allergic had a median specific IgE level of 98 kU/L for α -lactalbumin, 115 kU/L for β -lactoglobulin, and 138 kU/L for casein. In 1 of the 28 children who received HE OIT with DEW, severe symptoms (wheezing, generalized urticaria, rhinitis) appeared during the desensitization procedure, and the administration was stopped at the dose of 3 mg (IgE level of 95.8 kU/L at baseline).

AEs that Did Not Lead To Discontinuation

Thirty-five patients successfully completed the CM OIT, independent of the protocol. Twelve of these patients had mild-to-moderate AEs during the up dosing phase, and no symptomatic treatment was applied in the five patients with mild reactions. Seven patients had moderate AEs and received inhaled salbutamol and/or topical nasal steroids and/or cetirizine. In the group under the maintenance regimen, eight had mild-to-moderate AEs, in particular, during sport activities, exercise, viral or bacterial infections, or menses. None of these children discontinued CM intake (Table 2). In the HE OIT group, 27 patients completed the study

protocol. Three patients had mild reactions, and two had moderate reactions but continued the active treatment. During the maintenance egg-containing diet, after DEW desensitization, three patients had AEs during exercise or respiratory tract infection but carried out the postdesensitization follow-up. Among the children who were desensitized with whole egg, there were only three patients with mild reactions, and no treatment was required. During the maintenance phase, a girl had local urticaria during menses, but she continued the egg-containing diet (Table 2).

DISCUSSION

Apart from the efficacy of the tolerance induction, which is achieved in ~75% of patients,¹² the safety of the procedure remains a major concern.^{2,3,13} We reported herein the data derived from our 10-year experience with CM and HE OIT. We carefully examined the frequency and nature of AEs during up dosing and maintenance phases. Severe AEs that led to the discontinuation of the procedure were not rare (~9%). However, mild-to-moderate AEs could be easily managed by symptomatic drugs, without discontinuing the OIT protocol. In addition, we attempted to consistently grade AEs caused by OIT, with the aim of achieving an appropriate and reproducible reporting system. AEs during OIT are reported frequently: in some studies, up to 100% of patients experienced AEs during desensitization with CM,⁶ but OIT had to be discontinued in <20% of subjects.

The rate of AEs with HE OIT is also reported to be high (78%), with a study dropout rate of ~10%,² but a successful HE OIT could be achieved in 80% of patients. The discontinuation of the remaining subjects was associated with underlying asthma, high specific-IgE, and a lower threshold at oral food challenge. OIT peanut-based studies reported a rate of AEs similar to those carried out with milk or egg. However, the patients who underwent peanut OIT had more problems with the regular daily consumption of food during the maintenance phase. A recent study reported that >80% of patients treated with peanut OIT had to discontinue the treatment by the end of the third year.¹³

It is reasonable to think that more flexible OIT maintenance regimens are possible, at least for children who achieved a desensitization to CM. One study showed that the achieved tolerance to milk can be maintained without a mandatory daily consumption.¹¹ The rate of interruption of OIT in our survey (9%) seemed lower than in other studies. However, our trials were performed with slow up dosing regimens. Overall, the appearance of AEs during OIT was frequent, but only a minority of patients had to stop the active treatment. During the maintenance phase, one patient interrupted CM OIT due to the onset of eosinophilic esophagitis. The onset of eosinophilic esophagitis after OIT is re-

Table 2 Safety data in the whole population that received active CM or HE OIT during buildup (induction) and maintenance phases

	Mild	Moderate	Severe (OIT stopped)	Description
CM (<i>n</i> = 40)				
Buildup	5	7	4	Anaphylactic shock Abdominal pain, gritty eye Sneezing, cough, nausea
Maintenance	4	4	1	Esophagitis Angioedema, wheezing, urticaria (3, sport activity; 4, acute viral infection; 1, menses)
HE (<i>n</i> = 28)				
Buildup	3	2	1	Anaphylactic shock Facial erythema, mouth itching Vomiting, localized urticaria
Maintenance	3			Localized urticarial, abdominal pain

CM = Cow's milk; HE = hen egg; OIT = oral immunotherapy.

ported in 2.7% of patients with IgE-mediated food allergy.¹⁴ Due to the small number of treated patients in controlled trials, it was not possible to clearly identify risk factors, although a high allergen-specific IgE level was observed in subjects with severe AEs. Also, the vast majority of children, but one, who achieved maintenance OIT continued the treatment follow-up.

CONCLUSION

Our 10-year experience on AEs caused by OIT in children and adolescents was described herein. Based on the results, when also considering the prevalence and importance of food allergy,¹⁵ it seemed clear that such a procedure produced relevant beneficial effects,¹⁶ but it should be practiced only in a hospital or in an outpatient setting by physicians and nurses who are well trained in the field of OIT.

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