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The safety of oral immunotherapy for food allergy during maintenance phase: Effect of counselling on adverse reactions

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To the Editor,

Oral immunotherapy (OIT) can effectively induce a clinical desensitization in patients with persistent IgE-mediated food allergy (FA) to cow's milk (CM), hen's egg (HE), and peanut allergy.[1,2] However, its safety remains one of the major concerns, as adverse reactions (ARs) are quite frequent, unpredictable and unexpected.[1,2] ARs can occur with a previously tolerated dose of the offending food during the maintenance phase of desensitization, usually managed at home, and mainly during exercise,[3] viral illness or suboptimal asthma control.[4]

To assess the impact of a specific counseling and a specific written plan to avoid or reduce ARs occurrence during the maintenance regimen, we performed a retrospective cohort study. We collected retrospectively the clinical records of all the children who received OIT for CM or HE allergy at the Pediatric Allergy Unit of the University of Messina (Italy). We divided the population into two groups: Group A (n = 62), successfully desensitized between 2004 and 2012 but not receiving specific counseling and written plan about the possible ARs -due to the lack of knowledge on ARs at that time- and Group B (n = 34) successfully desensitized between 2013 and 2016, receiving counseling and a written plan on how to avoid or reduce ARs during the home-based maintenance regimen (Table 1**).** All the participants were eligible for OIT, according to clinical history, persistence of FA symptoms over time, and documented IgE-sensitization to CM or HE. The OIT protocols used and the follow-up modalities are reported elsewhere.[5,6] Briefly, food dose was weekly increased until the maintenance dose was achieved. This build-up phase was always performed in our Unit under medical supervision. Then, the maintenance phase was carried out at home. The OIT procedure and the risks of ARs were explained in detail to patients and their families. All procedures were approved by the ethical review board of Medical University of Messina (Messina, Italy) and a written informed consent was obtained from parents or legal guardians. The patients and caregivers were provided with an emergency kit including: written anaphylaxis emergency action plan, medications for self-treatment (corticosteroids, H1-antihistamines, short-term beta2agonist) and adrenaline auto-injector. Our clinical records, as per protocols, reported in detail: demography, diagnostic procedures, prescription, discontinuation and reason for, type and severity of ARs.[7,8]

Data were summarized as numbers (n) and frequencies (%) if they were categorical and as mean/median and standard deviation (SD)/ interquartile range (IQR) if quantitative. A paired Student *t*-test was used to compare the two groups and timing. These statistical tests were conducted using Prism software, version 6.0 (GraphPad, La Jolla, CA, USA). A P-value$<$0.05 was considered statistically significant.

Overall, 96 children underwent OIT for CM or HE. Group A included 62 patients, 35 desensitized for CM and 27 for HE between 2004 and 2012 (18 male, age range 4–13 years) and Group B included 34 patients, 10 desensitized for CM and 14 for HE between 2013 and 2016 (17 male, age range 4–14 years) (Table 2). No significant baseline differences were in age, food-specific IgE levels, skin test results, or oral food challenge (OFC) results between groups (Table 2). In Group B, there was a significant reduction in ARs versus Group A during the maintenance phase (p = 0.002). Before the introduction of counseling and written plan, 13/ 62 patients (21%) in Group A had mild to severe ARs during sport

Table 1
Written instructions for at home management of OIT.

Instructions
• Do not take the dose with empty stomach
• Avoid going to bed at least in the two hours after the dose
• Avoid exercise or sport activity for at least 2 hours after food intake
• If infections, asthma exacerbation, gastrointestinal diseases, / or menses: reduce or stop the dose of foods during acute phase, at least for 3 days

Abbreviations: AR, adverse reaction; CM, cow's milk; FA, food allergy; HE, hen's egg; IQR, interquartile range; OFC, oral food challenge; OIT, oral immunotherapy; SD, standard deviation.

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Table 2
Characteristics of study population.

	Group A (n = 62)				Group B (n = 34)			
	Cow's milk		Hen's egg		Cow's milk		Hen's egg	
	Median/n	IQR/%	Median/n	IQR/%	Median/n	IQR/%	Median/n	IQR/%
Patients (n,%)	35	*56*	27	*44*	20	*59*	14	*41*
Male (n,%)	18	*29*	15	*24*	11	*32*	6	*18*
Age (y) (mean ± SD)	8.9 ± 2.3		7.3 ± 2.6		7.9 ± 2		7.7 ± 2	
Caucasian (n, %)	35	*56*	27	*44*	20	*59*	14	*41*
Other allergic comorbidities								
Additional food allergies (n, %)[a]	3	*5*	6	*10*	1	*3*	3	*9*
Allergic asthma (n, %)	11	*18*	7	*11*	6	*18*	4	*12*
Allergic rhinitis (n, %)	10	*16*	11	*18*	7	*21*	5	*15*
Atopic dermatitis (n, %)	7	*11*	4	*6*	3	*9*	2	*6*
Food specific data								
Baseline IgE (kU/L), median (range)[b]	32.5	*(8.2-126)*	36.5	*(5-110)*	25.8	*(5.5-98)*	38.5	*(4.3-98.6)*
Baseline SPT wheal diameter (mm), median (range)[b]	7	*(5-15)*	11	*(7-20)*	7	*(5-16)*	9	*(6-17)*
Baseline OFC successfully consumed dose (mg), median (IQR)[b]	13.2	*(0-105.6)*	0.8	*(0-100)*	6.6	*(0-105.6)*	1.5	*(0-100)*
Clinical presentation (baseline OFC)								
Anaphylactic shock (n, %)	8	*13*	9	*15*	4	*12*	5	*15*
Asthma (n, %)	9	*15*	6	*10*	5	*15*	4	*12*
Diarrhea (n,%)	4	*6*	4	*6*	2	*6*	3	*9*
Rhinitis (n, %)	17	*27*	11	*18*	10	*29*	7	*21*
Urticaria (n, %)	15	*24*	19	*31*	9	*26*	10	*29*
Vomiting (n,%)	10	*16*	13	*21*	5	*15*	5	*15*
AR(s) during maintenance phase								
Mild-moderate ARs (n, %)	4	*6*	0	*0*	1	*3*	0	*0*
Mild-moderate ARs per patient, median (IQR)	3	*(2.25-4.5)*	0	*(0-0)*	0	*(0-0)*	0	*(0-0)*
Severe ARs (n, %)	5	*8*	3	*5*	0	*0*	0	*0*
Severe ARs per patient, median (IQR)	2	*(1-2.5)*	3	*(2-5)*	0	*(0-0)*	0	*(0-0)*
Eosinophilic Esophagitis (n,%)	1	*2*	0	*0*	0	*0*	0	*0*
Total Patients with ARs (n, %)[c]	10	*16*	3	*5*	1	*2*	0	*0*

Data were summarized as numbers (n) and frequencies (%) if they were categorical and as mean/median and SD/IQR if quantitative.
All characteristics were not statistically significantly different between groups and subgroups.
AR, Food-related adverse reaction; IQR, Interquartile range; OFC, oral food challenge; SPT, skin prick test.
[a] Includes egg (when different from OIT food), milk (when different from OIT food), tree nuts, fish, and wheat.
[b] Values referred to cow's milk or hen's egg according to the respective group.
[c] P values were statistically significant for comparisons between total patients with ARs (group A vs group B, p = .002); cow's milk and hen's egg subgroups were combined for the analysis.

activities, viral or bacterial infections, or menses. After the use of counseling and written instructions (2013–2016), the rate fell to 1/34 (3%) (p = 0.002) (Table 2). Within Group B, 18 patients (53%) had regular sport activity, five girls (15%) completed the pubertal stage, 20 (59%) suffered from acute infections (18 upper and/or lower respiratory tract, 1 skin, 1 urinary tract), but no severe ARs was reported. Only one patient in Group B, during OIT maintenance reported abdominal pain and generalized urticaria after sport activity. He ate 150 mL of milk 1 h before playing football. After this single episode, he continued the maintenance protocol. Of note, one of those patients desensitized to CM, during maintenance phase had frequently nausea, vomiting, dysphagia. An endoscopic biopsy specimen of the upper digestive tract showed a cellular infiltrate (>20% of eosinophils) in the esophageal epithelium, with intracellular edema and basal zone hyperplasia. In the two groups, only this patient had to stop the maintenance phase because of the diagnosis eosinophilic esophagitis.

The percentage of patients who successfully complete an OIT course and who achieve a full tolerance ranges between 35% and 100%.[7,8] Thus, safety remains a major concern of the procedure. It is currently not clear if a prolonged intake of the responsible food is needed to maintain tolerance, and in such cases the maintenance (regular assumption) is obviously managed at home, with possible additional safety problems. However, the so called "ad libitum diet" may be unpleasant above all for uncommon food. The frequency and grading of ARs during the up-dosing regimen was previously assessed,[8] but ARs can occur also during maintenance phase.[1,2,8] In addition, the setting of infection, sport exercise or menses are described frequent causes of acute ARs, or temporary relapse of FA during the maintenance or post-desensitization phases.[1–4] In the present report, we evaluated if an adequate counseling could reduce the ARs occurrence during the maintenance phase. The occurrence of ARs decreased from 21% to 3%, when written instructions were regularly given. Overall, only one patient out of 34 who received the instructions had moderate ARs, and none discontinued OIT. A limitation of this study stands in the retrospective study design, partly justified by the fact that the risk factors were identified only "a posteriori". However, data are complete, since, according to OIT protocols, they were accurately collected and patients regularly attended follow-up visits. In the present retrospective analysis, we confirm that ARs during post-desensitization phase of OIT can be minimized by providing few simple written instructions. These include avoiding physical activity within 2 hours of food intake, and reducing or interrupting the food intake during febrile illness. As per good clinical practice, all patients should be provided with an emergency action plan and auto-injectable adrenaline. Asthma, when present, should be adequately controlled with standard of care therapy.[9] With proper information and a structured written instruction plan, the risk of possible adverse reactions during the maintenance phase of food desensitization can be significantly reduced, still maintaining the beneficial effect of treatment.

Clinical implication

Safety is one of the major concerns of oral immunotherapy for IgE-mediated food allergy.

Proper information and a structured written instruction plan can significantly reduce the risk of adverse reactions during the maintenance phase of oral immunotherapy, still maintaining the beneficial effect of treatment.

Conflicts of interest

Nothing to disclose for all Authors.

Authors' contributions

SA, GBP and GP wrote the first draft of the manuscript. LC and GC reviewed the manuscript. All authors read and approved the final manuscript.

Declarations

Ethics approval and consent to participate: Letter of ethical clearance was secured from ethical review board of Medical University of Messina. Privacy and confidentiality of medical information was ensured. Moreover, written informed consent of patients was obtained prior to data collection.

Consent for publication: Not applicable.

Availability of data and material: The datasets generated during the current study are available from the corresponding author on reasonable request.

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References

1. Nurmatov U, Dhami S, Arasi S, et al. Allergen immunotherapy for IgE-mediated food allergy: a systematic review and meta-analysis. *Allergy*. 2017;72:1133–1147.
2. Pajno GB, Fernandez-Rivas M, Arasi S, et al. EAACI Guidelines on allergen immunotherapy: IgE-mediated food allergy. *Allergy. Allergy.* 2018;73:799–815.
3. Caminiti L, Passalacqua G, Vita D, Ruggeri P, Barberio G, Pajno GB. Food exercise induced anaphylaxis in a boy successfully desensitized to cow milk. *Allergy*. 2007;62:335–336.
4. 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.
5. 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.
6. Caminiti L, Pajno GB, Crisafulli G, et al. Oral Immunotherapy for egg allergy: a double blind placebo controlled study, with postdesensitization follow up. *J Allergy Clin Immunol Pract*. 2015;3:532–539.
7. Pajno GB, Caminiti L, Chiera F, et al. Safety profile of oral immunotherapy with cow's milk and hen egg: a 10-year experience in controlled trials. *Allergy Asthma Proc*. 2016;37:1–5.
8. Passalacqua G, Nowak-Wegryzin A, Canonica GW. Local side effects of sublingual and oral Immunotherapy. *J Allergy Clin Immnol Pract*. 2017;5:13–21.
9. Global Initiative for the Management of Asthma 2016 (GINA). www.ginasthma.org. Last accessed February 2017.

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