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

A R T I C L E   I N F O

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Cow's milk
Desensitization
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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. However, its safety remains one of the major concerns, as adverse reactions (ARs) are quite frequent, unpredictable and unexpected. 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, viral illness or suboptimal asthma control.

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. 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.

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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Regimen was previously assessed, but ARs can occur also during main-

tenance phase. In addition, the setting of infection, sport exercise or

menses are described frequent causes of acute ARs, or temporary relapse
development. As per good clinical practice, all patients should be provided with

oral food challenge; SPT, skin prick test.

Data were summarized as numbers (n) and frequencies (%) if they were
categorical and as mean/median and SD/IQR if quantitative.

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        |
| Patients (n,%)          | Median/n IQR/%   | Median/n IQR/%   | Median/n IQR/%   | Median/n IQR/%   |
| Male (n,%)              | 18/29            | 15/24            | 11/32            | 6/18             |
| Age (y) (mean ± SD)     | 8.9 ± 2.3        | 7.3 ± 2.6        | 7.9 ± 2.2        | 7.7 ± 2.2        |
| Caucasian (n, %)        | 35/56            | 27/44            | 20/59            | 14/41            |
| Other allergic comorbidities |                 |                  |                  |                  |
| Additional food allergies (n, %) | 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) | 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) | 7 (5-15)         | 11 (7-20)        | 7 (5-16)         | 9 (6-17)         |
| Baseline OFC successfully consumed dose (mg), median (IQR) | 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

|                        | Group A (n = 62) | Group B (n = 34) |
|------------------------|------------------|------------------|
| Mild-moderate ARs (n, %) | 4/6              | 0/0              | 1/3              | 0/0              |
| Severe ARs (n, %)       | 5/8              | 3/5              | 0/0              | 0/0              |
| Total Patients with ARs (n, %) | 10/16            | 3/5              | 1/2              | 0/0              |

activities, viral or bacterial infections, or menses. After the use of coun-

seling 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 gener-
alized 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

the risk factors were identi-
ed 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 in-

structions. 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.

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 ben-

eficial 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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