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Long-term outcome of omalizumab-assisted desensitisation to cow's milk and eggs in patients refractory to conventional oral immunotherapy: real-life study

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Abstract
Background: Oral immunotherapy (OIT) is a promising approach to cow's milk and egg allergies, but reactions are frequent and some patients cannot be desensitized.
Objective: To evaluate long-term OIT outcomes with omalizumab (OMZ) in paediatric patients with severe egg and/or milk allergies.
Methods: This retrospective real-life study analysed findings in children with Immunoglobulin E-mediated allergy to cow's milk and/or hen eggs refractory to conventional OIT, who underwent OIT with OMZ in our department between 1 January 2010 and 31 December 2015.
Results: In all, 41 patients were included (median age: 7 years; interquartile range [IQR]: 5.5-9.5); 26/41 (63.4%) underwent OIT for milk, 8/41 (19.5%) for egg and 7/41 (17.1%) for both. The median time between initiation of OMZ and OIT was 27 weeks (IQR: 22-33). Forty (97.56%) patients reached the maintenance phase (200 mL of cow's milk and 30 mL of raw egg or 1 cooked egg) in a median time of 27 weeks (IQR: 18-37). The median total time with OMZ was 117 weeks (IQR: 88-144). During the OMZ period, 2.44% (1/41) of patients presented anaphylaxis. After discontinuation of OMZ, 29.3% (12/41) presented anaphylaxis, 50% of them had a poor adherence to daily ingestion. One patient (2.44%) was diagnosed with eosinophilic esophagitis after 2 years of discontinuation of OMZ. Currently, after a median time of 9 years (IQR: 7-10) since the initiation of OMZ, 75.6% (31/41) are desensitized (27/31 without OMZ).
Conclusions: Omalizumab allows desensitisation of children with severe allergies to cow's milk and/or egg without developing severe reactions while receiving this treatment. However, discontinuation of OMZ leads to severe allergic reactions, and hence must be monitored carefully.

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Introduction

Allergies to cow's milk (CM) and hen eggs are among the most common food allergic manifestations in children, and there is evidence of an increasing prevalence and greater persistence of food allergies.[1] The mainstay of treatment is avoidance of these products, which is difficult, provided the ubiquitous nature of milk and eggs, leading to frequent and often severe allergic reactions (AR).[2] Oral immunotherapy (OIT) is an alternative to avoidance of diets, and some recent clinical practice guidelines have explained how to manage OIT.[3,4] OIT is an efficacious experimental approach to food allergies and has been indicated to provide substantial benefits in terms of allergen desensitisation. However, this therapy is associated with high rates of allergic reactions.[5] Indeed, up to 20–30% of food allergic patients are refractory to desensitisation, particularly those with higher initial food-specific immunoglobulin E (IgE) levels.[6]

In order to mitigate the risks of OIT, and potentially enhance its efficacy, several trials have studied the use of omalizumab (OMZ) (Xolair®, Novartis) as an adjuvant treatment for patients undergoing OIT.[7-10] OMZ is a humanised, recombinant, monoclonal antibody which binds to free-serum IgE antibodies and consequently prevents their binding to the high-affinity IgE receptor, FcεRI, on effector cells such as mast cells and basophils. The Food and Drug Administration (FDA) has currently approved OMZ for the treatment of allergic asthma and chronic urticaria, because it has demonstrated to reduce allergic reactions with aeroallergen immunotherapy.[11]

Over the last decade, OMZ has also been studied as an off-label treatment or adjunct to treatment for numerous allergic manifestations, including allergic rhinitis, food allergies, atopic dermatitis, eosinophilic gastrointestinal disease, idiopathic anaphylaxis, mastocytosis and allergic bronchopulmonary aspergillus.[12]

Omalizumab has been depicted to increase allergen threshold in patients with food allergies.[13] In order to leverage the benefit of having shortened dosing schedules and reducing allergic reactions, this drug has been used in combination with OIT. Several studies have demonstrated that OIT in combination with OMZ reduces allergic reaction and its severity, establishing its improved safety profile against OIT alone. This benefit is even more prominent in patients with history of several anaphylaxis whose OIT had failed because of allergic reactions. Nonetheless, patient evolution after discontinuation of OMZ remains to be studied thoroughly.

Omalizumab has been used in our centre for years as an off-label indication independent of the technical data sheet in patients unresponsive to conventional OIT. This study aimed to evaluate the long-term safety and efficacy of OIT with OMZ in paediatric patients with severe allergies to egg and/or milk.

Material and methods

Study population and design

This retrospective real-life study included paediatric patients (aged ≤15 years) with IgE-mediated allergy to cow's milk (CM) and/or hen eggs. These patients were refractory to conventional OIT, and underwent OIT with OMZ between January 2010 and December 2015. The patients were subsequently followed at our centre for at least 5 years.

We considered refractory patients to OIT who either had recent documented anaphylaxis after accidental ingestion or systemic reaction to a minimal dose during oral food challenge (OFC) prior to initiating OIT.

The interval between the reaction and inclusion in the study was less than or equal to 6 months. Omalizumab was used off-label as a compassionate access protocol in patients not having severe asthma.

This study was approved by the local medical ethics committee of the Parc Taulí Hospital Universitari. Patient data were recorded, stored and analysed in accordance with confidentiality regulations (EU 2016/679).

Omalizumab initiation phase

Prior to starting OMZ, total IgE and specific IgE values (for cow's milk allergy: cow's milk, casein, alpha-lactalbumin and beta-lactoglobulin; for egg allergy: egg, ovomucoid and ovalbumin) were obtained with ImmunoCAP™ (Thermo Fisher Scientific, Barcelona). Laboratory processing truncated the values of specific IgEs as >100 kU/L to 100kU/L.

An endpoint titration skin prick test (SPT) was also performed using serial 10-fold dilutions of milk and/or egg extracts (1:1000, 1:100, 1:10 and pure specimen). Negative (saline solution) and positive (histamine chlorhydrate 1%) controls were also included.

As an off-label indication, the dose and administration interval of OMZ were based on the manufacturer's recommendations for treating severe allergic asthma.

The half-life of OMZ is 3–4 weeks,[14] and therefore it is estimated that minimum 9 weeks are required to achieve maximum effect to reduce both circulating IgE and expression of its receptors. To evaluate the effects of anti-IgE therapy on SPT responses, the endpoint titration SPT was repeated after having received OMZ for 4 months and then every 2 months until the components were observed to be less than histamine, and then OIT was initiated. In case of patients having asthma, OIT was not started until the asthma was controlled.

Initiation of oral immunotherapy

Prior to initiating desensitisation, an open OFC was performed in our paediatric day hospital. This was exercised following our standard protocol.[15] Patients were initially given 0.1 mL of fresh pasteurised cow's milk or pasteurised liquid raw egg white, followed by increasing doses every half an hour over several hours to identify dose toleration. Throughout OFC, vital signs were checked, and pertinent physical examination were repeated at least every 30 min at clinician's discretion. The supervising physician discontinued OFC if clinical reaction appeared and medications were administered as required. Daily home dose was continued with the highest dose tolerated on the dose escalation day.

During the build-up phase, the daily dose was increased by weekly or biweekly increments until the target dose (200 mL of cow's milk and 30 mL of raw egg white or 1 cooked egg) or the maximum tolerated dose was attained,

with modifications in patients who developed reactions. All dose escalations were conducted under physician's supervision in our paediatric day hospital.

Discontinuation of omalizumab and oral immunotherapy maintenance

At the end of the build-up phase, the patients achieved desensitisation, in which hyporesponsiveness was maintained with regular ingestion of food that could be lost with even brief interruption in doses. In the maintenance phase, children continued receiving the maintenance dose (cow's milk: 200 mL; egg: 30 mL of raw egg white or 1 cooked egg) or the highest dose tolerated, once a day or at least thrice per week, without interruption, along with unrestricted access to any food containing egg or milk.

If the patient did not report symptoms 4–6 months after reaching the maintenance dose, OMZ was gradually reduced by increasing the time interval between doses by 25–50% while caring to avoid failure in the desensitisation already achieved. Meanwhile, patients were reminded to continue taking cow's milk and/or eggs on a daily basis or for a minimum of thrice a week.

Figure 1 presents a summary of OIT with OMZ protocol.

Safety and efficacy variables of oral immunotherapy with omalizumab

The safety of OIT is one of the most important factors to be considered if applying the evidence obtained in studies to the clinical practice setting. To assess safety and efficacy, the following data were considered:

1. *Anaphylactic reactions*. We recorded all anaphylactic episodes presented during the escalation, build-up phase and maintenance phases with OMZ and without OMZ. In cases presenting anaphylaxis, possible cofactors or poor adherence to the maintenance dose were recorded.
2. *Eosinophilic esophagitis (EoE) with OIT*. Development of eosinophilic esophagitis has been reported during OIT. Therefore, we registered the number of patients diagnosed with this disease during and after OIT.
3. *Efficacy of desensitisation*. This is defined as a temporary increase in the threshold of reactivity, with maintenance of the desensitized state requiring continued consumption of allergenic protein to prevent the reappearance of reactivity. The following two subtypes of desensitisation were considered:
   - *Complete desensitisation* (CD): If the patient is able to tolerate the full-serving dose, which is equal to 200 mL of cow's milk and 30 mL of raw egg or one cooked egg.
   - *Partial desensitisation* (PD): If the patient is not able to tolerate a full-serving dose but their tolerance threshold improved compared to their tolerated dose before OIT. Maintenance of partial desensitisation was justified to avoid allergic reactions caused by accidental ingestion of minimal food dose.

   The data were evaluated after reaching the maintenance phase and at the last follow-up visit, which was at least 5 years after starting OIT.
4. *Sustained unresponsiveness* (SU). This term describes patient's ability to pass an OFC after discontinuing OIT. Most studies have demonstrated that the majority of patients treated with OIT can be successfully desensitised to a particular food. However, there are few studies demonstrating sustained unresponsiveness. As this was a real-life study, we recorded the number of

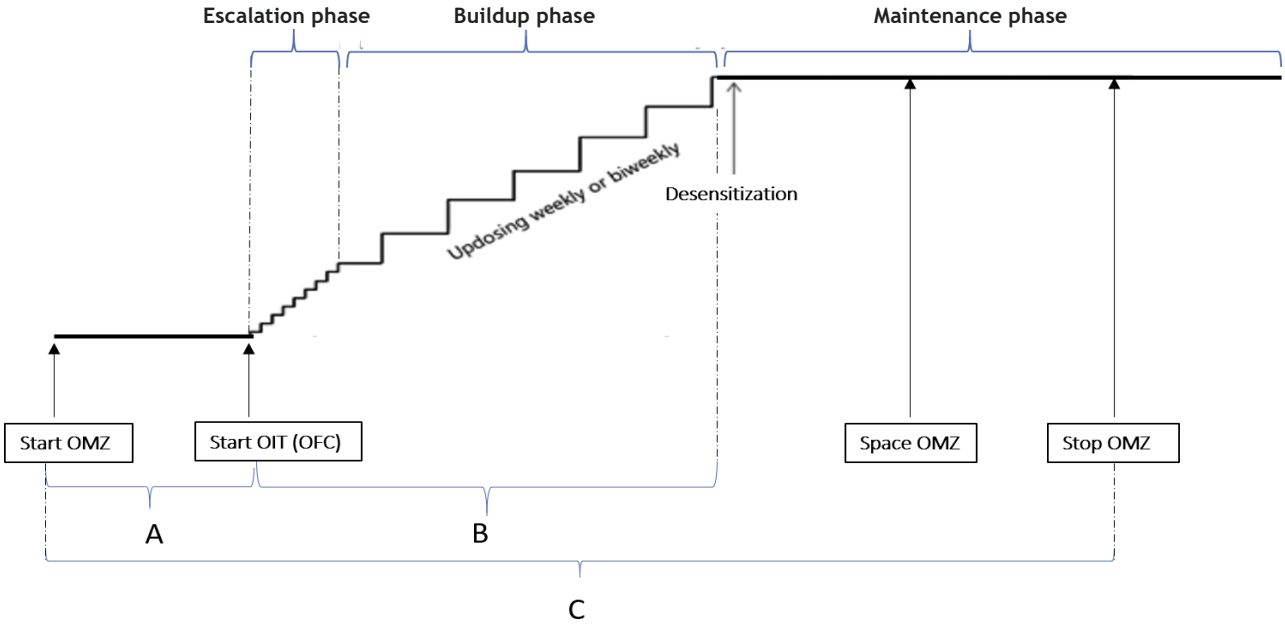

Figure 1 Protocol of oral immunotherapy with omalizumab. OIT: oral immunotherapy; OMZ: omalizumab; OFC: oral food challenge. A: Timing of OMZ use pre-OIT; B: time between initiation of OIT and achieving the maintenance dose; C: time between start and discontinuing of OMZ.

patients undergoing an OFC after a period of time without taking the allergenic food and whether an allergic reactions was presented or not.

Statistical analysis

Categorical variables are expressed as frequencies and percentage values. Continuous variables are expressed as medians and interquartile range (IQR). Statistical significance was set at $P < 0.05$. We used SPSS 25.0 for Windows (IBM, Armonk, NY, USA) to conduct all analyses.

Results

Population characteristics

Figure 2 shows a flowchart of 41 patients included in this study. The median age of the participants was 7 years (IQR: 5.5–9.5) at the initiation of OMZ, and 65.8% (27/41) were males. Of the 41 patients, 26 (63.4%) underwent OIT with OMZ to milk, 8 (19.5%) to egg and 7 (17.1%) to milk and egg. Table 1 shows the characteristics of these patients. Most (92.7%) of the patients had allergy-related comorbidities: 87.8% had asthma, 61.0% had allergic rhinitis, 39.0% had atopic dermatitis and 26.8% had other food allergies. The IgE levels were as follows: median total IgE: 330 kilounits of allergen-specific IgE per liter (KUA/L), milk IgE: 38.1 KUA/L, casein IgE: 35.9 KUA/L, egg IgE: 10 KUA/L and ovomucoid IgE: 17.45 KUA/L. The median SPT to milk, casein and ovomucoid was 8 mm and that to egg was 7 mm.

Timing of OMZ use pre-OIT and up-dosing phase

The median time between the initiation of OMZ and OIT (time A in Figure 1) was 27 weeks (IQR: 22–33; milk: 26, egg: 29). The wheal diameter was significantly decreased in response to an SPT with pure extracts of cow's milk, casein, egg and ovomucoid between initiation of OMZ and OIT ($P < 0.05$; Table 2).

The mean cumulative tolerated dose of OFC prior to OIT with OMZ was: 15.80 mL (IQR: 1.0–9.0) for cow's milk and 4.45 mL (IQR: 0.1–3.3) for pasteurized liquid raw egg white. No patient required treatment with epinephrine during the baseline food challenge.

All the patients reached maintenance phase (time B in Figure 1) within a median time of 26 weeks (IQR: 18–37; milk: 26, egg: 24).

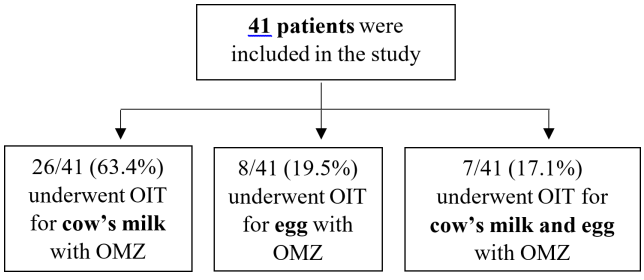

Figure 2 Flow chart of study design. OIT: oral immunotherapy; OMZ: omalizumab

Length of OMZ therapy

The median total time for OMZ (time C in Figure 1) was 122 weeks (IQR: 101–117; milk: 187, egg: 172). Of the 41 patients, 13 (31.71%) had to restart OMZ due to the reappearance of symptoms. Currently, after a median time of 9 years (IQR: 7–10) since the initiation of OMZ, 4/41(9.76%) patients are receiving OMZ.

Safety and efficacy assessments

During the build-up phase, only one patient (2.44%) presented anaphylaxis with OMZ. However, no patient presented anaphylaxis during the escalation and maintenance phases with OMZ. After discontinuation of OMZ, 12 patients

Table 1 Characteristics of the subjects included in the study.

Male, n (%)	27 (65.9)
Age (y), median (IQR)	7 (5.5 -9.50)
Asthma, n (%)	36 (87.8)
Allergic rhinitis, n (%)	25 (61.0)
Atopic dermatitis, n (%)	16 (39.0)
Other food allergies, n (%)	11 (26.8)
Total IgE (kUA/L), median (IQR)	330 (155–978)
Baseline milk IgE (kUA/L), median (IQR)	38.1 (20.92–96.97)
Baseline caseine IgE (kUA/L), median (IQR)	35.9 (16.65–98.23)
Baseline egg IgE (kUA/L), median (IQR)	10 (8.33–100.00)
Baseline ovomucoid IgE (kUA/L), median (IQR)	17.45 (7.28–85.23)
Baseline milk prick test score (mm), median (IQR)	8 (6.0–9.5)
Baseline casein prick test score (mm), median (IQR)	8 (6.5–11.5)
Baseline egg prick test score (mm), median (IQR)	7 (6.0–9.0)
Baseline ovomucoid prick test score (mm), median (IQR)	8 (7.0–8.0)

IQR: interquartile range; KUA/L: kilounits of allergen-specific IgE per liter.

Table 2 Results of skin prick test.

Skin prick test	Baseline (prior to initiating OMZ)	Prior to initiating OIT, after starting OMZ	P
Milk SPT (mm), median (SD)	8 (2.80)	5 (2.85)	<0.001
Casein SPT (mm), median (SD)	8 (3.27)	4 (2.01)	0.002
Egg SPT (mm), median (SD)	7 (1.51)	6 (1.46)	0.039
Ovomucoid SPT (mm), median (SD)	8 (2.93)	5 (1.60)	0.017

OMZ: omalizumab, OIT: oral immunotherapy, SD: standard deviation.

(29.26%) had anaphylactic reactions: 11 patients (26.82%) presented one episode and 1 patient (2.44%) presented two episodes of anaphylaxis. Two of these 13 (15.38%) episodes of anaphylaxis were related to the effect of cofactors (when ingestion of cow's milk was immediately followed by exercise). In six of these 12 patients, the presentation of anaphylaxis was related to poor adherence to daily ingestion or a period of time without taking the allergenic food. In addition, we observed that most of the patients (9/12, 75%) who presented an anaphylactic reaction during the maintenance phase were allergic to cow's milk and 33.3% (3/9) had a reaction with the intake of cheese, potentially because of a large content of protein in cow's milk.

Only one of the 41 patients (2.44%) presented EoE, being diagnosed 5 years after starting OIT and 2 years after discontinuing OMZ.

In relation to the efficacy of desensitisation, we observed that initially (upon reaching the maintenance phase), 97.56% (40/41) of the patients achieved complete desensitisation and only one patient (2.44%) had partial desensitisation. At the request of the family, the latter patient did not continue with complete desensitisation and had an intake of 80 mL of cow's milk. Currently, 75.60% (31/41) are still desensitized; 63.63% (28/41) having complete desensitisation and 7.31% (3/41) with partial desensitisation; however, four patients are still on OMZ, so 65.85% (27/41) remained desensitized without OMZ (after a median time of 6 years since discontinuation of OMZ). The remaining 24.39% (10/41) patients discontinued taking the food involved (milk or egg) (Table 3). Of the 10 patients who currently cannot tolerate food, in 30% (3/10) it was due to a history of anaphylaxis when OMZ was discontinued and in 50% (5/10) it was due to recurrent of mild reactions (especially gastrointestinal symptoms). It must be noted that 60% (6/10) of the patients who currently do not tolerate the allergenic food had poor adherence to daily ingestion, which is defined as consumption of the food involved (one egg or 200 mL of cow's milk) for less than thrice a week. Eight of the 12 patients who presented anaphylaxis continued treatment and were able to achieve desensitisation: complete desensitisation (7/12) and partial desensitisation (1/12).

In order to evaluate sustained unresponsiveness, 17/41 (41.46%) patients underwent an OFC after 4–8 weeks without taking the allergenic food. The mean period between reaching the maintenance dose and this OFC was 2.8 years (IQR: 2.0–3.8). Seven of these 17 patients (41.17%) demonstrated permanent tolerance and 10/17 (58.82%) had a positive OFC, while 4 of these 10 (40%) patients presented an anaphylactic reaction. This four patients were restarted OMZ for a period of time, and currently two of them are completely desensitisation without OMZ.

Table 3 Desensitisation data.

Desensitisation upon reaching the maintenance phase	
Complete desensitisation, n (%)	40/41 (97.56)
Partial desensitisation, n (%)	1/41 (2.44)
Currently desensitized (>5 years since the initiation of OMZ)	
Complete desensitisation (CD), n (%)	28/41 (63.63)*
Partial desensitisation (PD), n (%)	3/41 (7.31)*
No desensitisation, n (%)	10/41 (24.39)

*Four patients (three from CD and one from PD) are still on OMZ.
OIT: oral immunotherapy.

Discussion

To our knowledge, this is the first observational study reporting long-term outcomes for up to 5 years of OIT with OMZ in paediatric patients with severe allergies to egg and/or cow's milk. This real-life study demonstrated that most paediatric patients with severe allergies to cow's milk and/or egg, and were refractory to conventional OIT, could be desensitized with OMZ and OIT.

Within the context of severe food allergies, OMZ has been the most widely studied drug.[16] In patients receiving OMZ for asthma symptoms, Rafi et al. had described reduction in their concomitant IgE-mediated food allergy symptoms.[17]

Based on these outcomes, the authors concluded that OMZ could be a good therapeutic option for patients with high risk of severe reactions.[17] Presently, adjuvant therapy with OMZ is used in severe peanut, milk, egg and multiple food allergies in order to improve OIT safety profile and maintain or increase its efficacy.[8-10,18-26]

Omalizumab also allows more rapid desensitisation and has demonstrated to decrease the time to achieve maintenance dose.[19,23,26-28] In the present study, the median time for reaching the maintenance phase was 26 weeks (milk: 26, eggs: 24), similar to the results of the study conducted by Wood et al., which compared patients treated with OMZ with those receiving placebo in milk OIT.[9] They determined that time to the escalation phase was shortened with OMZ (median 25.9 vs. 30.0 weeks; $P = 0.01$).

The association with OMZ seems to solve the problem of safety of OIT and minimises the development of allergic reactions during the desensitisation process.[7-10,13,22,24,29] In the current study, only one patient presented severe reactions with OMZ, which corroborated the observation that OMZ might have a protective effect on adverse reactions.

While OMZ does seem to provide a protective effect, more than 40% of patients relapse, with a decrease in the clinical reactivity threshold at 2–4 months after discontinuation of treatment, suggesting the requirement for longer maintenance therapy with OMZ.[10,22,27]

In this study, OMZ was spaced and gradually discontinued according to tolerance, allowing more patients (75.60%) to tolerate allergenic food during long period. Nonetheless, some patients (29.26%) presented severe reactions when OMZ was discontinued. However, comparative analysis of allergic reactions with other studies of milk or egg OIT with OMZ was problematic, since patients in the present study were not representative of all OIT candidates of other studies, such as those conducted by Martorell et al.[10] and Lafuente et al.,[22] in which the patients had severe allergies and were refractory to standard OIT. The reactions presented during the maintenance phase were related to poor adherence to daily ingestion of the allergenic food or to the effect of cofactors, as have been described in previous studies.[30-33]

Only one patient (2.44%) was diagnosed with EoE. The rate of this disease in the present study was comparable to a systematic review with meta-analysis,[34] which reported

that new onset of EoE after OIT occurred in up to 2.7% cases; this outcome was lower than what was described by MacGinnitie et al.[18] and Brandström et al.,[25] who reported EoE in 8% cases.

Concerning long-term efficacy, desensitisation was achieved in 75.6% of patients (complete desensitisation: 63.6% and partial desensitisation: 7.3%) after a median period of 9 years (IQR: 7–10). This percentage was similar to that of a prospective study[35] evaluating the efficacy of a rush desensitisation protocol in 18 children allergic to cow's milk. This prospective study[35] found that 72% of the children achieved complete desensitisation after 2 years and were able to maintain a diet without restrictions.

Some studies have reported the development of sustained unresponsiveness after egg[36-39] and milk[9,32,37] OIT. These studies described sustained unresponsiveness in 36–50% of the population after 3–48 months of milk or egg OIT. These results were comparable with the present study, where sustained unresponsiveness was observed in seven of the 17 patients (41.17%), who were proposed to undergo OFC after OIT with a mean period of 33.6 months. However, it was noted that among those presenting a reaction to OFC after OIT, four (9.7%) patients had an anaphylactic reaction.

Oral immunotherapy causes anxiety in some patients and families, as it carries risk of allergic reactions. This emphasises the importance of performing OIT only in qualified centres with expertise for providing this treatment, and both family and patient must be well informed about OIT.

This intervention had an impact on both children and their families. We consider that it is crucial for these patients to be regularly followed, emphasising the importance of daily intake to guarantee the safety of treatment as well as awareness of active disease and the possibility of occurrence of allergic reactions. The cost of OMZ must also be considered. Therefore, patients must be selected carefully to ensure good adherence to treatment.

The main limitations of the present study were that its results represented the retrospective experience of a single centre. Nevertheless, in the absence of larger prospective studies on OIT with OMZ, our data could facilitate decision-making for clinicians treating patients with severe allergies to cow's milk or egg, who are refractory to conventional OIT.

Additional studies on the most appropriate maintenance dose and the length of OMZ and maintenance therapy are required to optimize this treatment. Given that food-related OIT does not consistently lead to sustained unresponsiveness, the benefits of protection against accidental exposure versus the risks of allergic reactions occurring during OIT must be balanced before considering the use of OMZ associated with OIT.

Conclusion

In conclusion, although OMZ still has no indications for food allergies, it may represent a safe and effective alternative treatment in a selected group of paediatric patients with severe allergies to cow's milk and/or egg and refractory to conventional OIT. However, discontinuation of OMZ can lead to allergic reactions, primarily related to poor adherence to daily ingestion. Hence, regular follow-up is important, emphasising the requirement for daily intake to guarantee safety of the treatment. Nevertheless, additional large studies are required to better understand the long-term benefits and risks of this treatment.

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