Allergologia et immunopathologia
Sociedad Española de Inmunología Clínica, Alergología y Asma Pediátrica
www.all-imm.com

ORIGINAL ARTICLE

OPEN ACCESS

Food oral immunotherapy: Any distinguishing factors predicting the need of anti-IgE?

Sanem Eren Akarcan[a]*, Handan Duman Şenol[b], Figen Gülen[b], Esen Demir[b]

[a]*Tepecik Training and Research Hospital, Pediatric Allergy and Immunology Clinic, İzmir, Turkiye*
[b]*Ege University Faculty of Medicine, Department of Pediatric Allergy and Immunology, İzmir, Turkiye*

Received 15 May 2023; Accepted 10 October 2023
Available online 1 November 2023

KEYWORDS
allergic reactions;
food allergy;
food challenge test;
omalizumab;
oral immunotherapy

Abstract
Oral immunotherapy (OIT) has gained popularity recently for IgE-mediated food allergy. Omalizumab (OMZ) has been used in patients (10-20%) who have too severe/frequent allergic reactions (AR) to continue OIT, to reduce these reactions. In this study, it was aimed to compare two groups of patients who completed OIT with and without OMZ and to seek determinants predicting the need of this treatment. It was also aimed to share the clinical findings regarding the long-term use of OMZ and the withdrawal process. Forty-one patients were started OIT and 93% could be desensitized. Two groups were similar in means of demographic characteristics, and clinical and laboratory findings. The patients who needed OMZ during OIT had also lower reaction doses during oral challenge ($p = 0.037$). Higher AR rate in this group declined after starting OMZ ($p < 0.001$). The injection intervals of OMZ were gradually extended. Most patients were able to discontinue OMZ (81%). There were no severe reactions during drug withdrawal attempts. The low reaction thresholds during oral food challenge may give a clue about OMZ requirement during OIT. It may be an option to start the treatment before OIT if reaction was seen in the first few steps of the oral food challenge. For the sake of safety, extension of injection intervals should be preferred instead of abruptly stopping OMZ.

Introduction

Oral immunotherapy (OIT) is a relatively new, promising treatment for IgE-mediated food allergy that aims to desensitize and, if possible, develop permanent tolerance to the allergen food by administering increasing doses of that food.[1] During OIT, IgE-mediated allergic reactions (AR) in different severities can be seen.[2] While most of the patients achieve to complete the process, 10-20% of them cannot continue the treatment due to these side effects.[1-3]

***Corresponding authors:** Sanem Eren Akarcan, Tepecik Training and Research Hospital, Pediatric Allergy and Immunology Clinic, İzmir, Turkiye. *Email address*: saneren@yahoo.com

https://doi.org/10.15586/aei.v51i6.907

After a very severe AR such as marked dyspnea or anaphylaxis, it is not easy to encourage the family to continue OIT without an alternative method. Even very frequent mild reactions can be annoying enough to quit the treatment.

Omalizumab (OMZ) binds to Fc portion of IgE which is also the binding site for IgE receptors (FCε RI and II). Via this binding process, OMZ sequesters free IgE and blocks its binding to the receptors. Moreover, OMZ accelerates the dissociation of receptor bound IgE from mast cells and basophils. As a result, IgE-related allergic responses and the number of eosinophils, mast cells, and basophils decrease.[4,5] This treatment had been approved for clinical use in severe allergic asthma and chronic spontaneous urticaria.[6] Although not in routine use, some uncontrolled and controlled trials demonstrated that anti-IgE therapy is effective in terms of increasing the reactivity threshold against food allergens and allowing safe and rapid desensitization.[7-10] However, questions remain regarding its optimal use in clinical practice.[11,12]

It is recommended that food allergen immunotherapy be performed only in centers with extensive experience in this field.[13] Our allergy department, as one of the few centers serving in this field in the country, has been applying OIT since 2008. In addition, OMZ has been used as an adjunctive therapy since 2017 in patients who would not be able to continue OIT due to allergic side effects. A decision to start OMZ is taken on a patient basis, considering the severity and frequency of ARs during OIT.

In this study, it was aimed to retrospectively evaluate the clinical and laboratory characteristics of patients undergoing OIT, to compare the patients who received OMZ treatment with the ones who did not in addition to OIT and thus to search for determinants predicting the need of OMZ. In addition, we aimed to share the data regarding the durations before and after OMZ treatment, and the intervals of OMZ for each patient who received OMZ (as a single-center experience).

Methods

Study Population

This is a retrospective study evaluating the food (milk and egg) allergic patients who received OIT in Ege University Pediatric Allergy Department between June 2017 and June 2022.

Hospital files of the patients were evaluated and clinical characteristics, results of the laboratory parameters and skin prick tests (SPT), data about the oral food challenge (OFC) test and OIT process were recorded.

This study was approved by the local ethics committee (Ege University Medical Faculty Ethics Committee No:20-12T/4).

Skin Prick Test

Skin prick tests were performed with fresh milk and egg white. Single-peak lancets (1 mm diameter) (Stallerpoint®, Stallergenes, SA, Laboratories) were used to prick the skin. Histamine (10 mg/ml) was used as positive control and NaCl (0.9%) was used for negative control. The wheal size for histamine and the foods were measured in millimeters (mm). A wheal size $\geq$ 3 mm larger than the negative control was accepted as positive.

Specific IgE Measurement

Serum total IgE and specific IgE (sIgE) levels for cow's milk, casein, beta-lactoglobulin and egg white were measured using the CAP system-FEIA (Pharmacia Upjohn, Uppsala, Sweden).

OFC Test

An open OFC test protocol was performed in all patients except those with an anaphylaxis within last 3 months. The tests were started using 0.5 ml of 1:10 diluted pasteurized CM (1.5 mg of protein) or 0.25 gram boiled egg white (27.5 mg of protein). The doses were increased every 15–30 minutes until an objective reaction was noted or the target steps of 100 ml milk (3300 mg of protein) or 15 g egg white (1650 mg of protein) were completed (Table 1). Test results were considered positive when at least one objective symptom such as urticaria/angioedema, airway obstruction signs (e.g. stridor, dyspnea, rales, and rhonchi), vomiting and anaphylaxis developed. Cumulative food protein content taken up to the stage of AR was calculated and recorded.

Oral Immunotherapy

The patients older than three years with a positive OFC test or a recent anaphylaxis (within last 3 months) were diagnosed as persistent food allergy. The parents of these patients were informed about OIT and asked to sign the consent form if they decided to start OIT. OIT was initiated the day after the OFC test according to the reaction step. Milk dose was determined as three steps behind the reaction dose (two steps behind for step 3). In the patients who developed a reaction in the first two steps or had a recent anaphylaxis with accidental intake, OIT was started with a dose of 0.5 ml of 1:100 diluted CM (0.15 mg of protein). Egg white was initiated with the same ordered OIT step as the reaction step of the OFC test. The patients continued to receive the same amount of milk or egg white daily at home for the following week. Dose increments were done in hospital every week according to the protocols until the target doses of 200 ml milk (6600 mg of protein) or 40 ml egg white (4950 mg of protein) were reached (dose escalation phase).[14,15] Ketotifen-a mast cell stabilizer and dual acting antihistamine- was used daily in all patients as an adjuvant therapy during this phase to prevent the mild reactions.[16] If the patient had an infection dose increment was not performed that week. If a dose was not tolerated, the patient received the last tolerated dose that week. Heavy exercise was prohibited for up to 2 hours after dose intake.[17] At the end of dose escalation phase, the patients continued to consume the target doses daily (maintenance phase).

Table 1 Oral food challenge test protocol for milk and egg white.

		Milk		Egg White	
Step	Minutes	Dose of the step milk (mL)/protein (mg)	Cumulative dose mL/mg	Dose of the step egg(g)/protein(mg)	Cumulative dose g/mg
1	0.	0.05/1.5	-	0.25/27.5	-
2	15.	0.1/3	0.15/4.5	0.5/55	0.75/82.5
3	30.	0.3/10	0.45/14.5	1/110	1.75/192.5
4	45.	0.6/20	1.05/34.5	2.5/275	4.25/467.5
5	60.	0.9/30	1.95/64.5	7.5/825	11.75/1292.5
6	90.	1.5/50	3.5/115	15/1650 (1/2 egg white)	26.75/2942.5 (~1 egg white)
7	120.	3/100	6.5/215	-	-
8	150.	6/200	12.5/415	-	-
9	180.	12/400	24.5/815	-	-
10	210.	24/800	48.5/1615	-	-
11	240.	50/1650	98.5/3265	-	-
12	270.	100/3300 (1/2 cup of milk)	198.5/6565 (~1 cup of milk)	-	-

Table 2 Severity grading of allergic reactions.

General severity grading of allergic reactions[2]		
Mild	Grade 1	Localized cutaneous erythema/urticaria/angioedema/oral pruritus
	Grade 2	Generalized erythema/urticaria/angioedema
	Grade 3	Gastrointestinal symptoms/rhinoconjunctivitis besides grade 1 or 2 reactions
Moderate	Grade 4	Mild laryngeal edema/mild asthma
Severe	Grade 5	Marked dyspnea/anaphylaxis
Numeric expression of reaction types seen in each patient		
1	Only mild reactions occurred	
2	Mild and moderate/severe reactions occurred together	
3	Only moderate/severe reactions occurred	

The time passed until maintenance phase and any adverse events throughout dose escalation and maintenance phases were recorded in detail. Severity grading of the adverse reactions was done according to Table 2.[2] In order to standardize the ARs that patients experienced, the AR rate was formulated as follows: *AR rate = numeric expression of AR types × number of ARs/time passed (weeks)* (Table 2).

OMZ Treatment

The patients who had moderate/severe or very frequent mild reactions which prevented the appropriate dose escalation and who would have to leave OIT were offered to continue OIT by adding OMZ. Permission for the off-label use of OMZ was granted from the Turkish Ministry of Health for each patient. The OMZ dosage chart recommended for pediatric asthma patients was used to determine the patients' OMZ dose (mg) and interval (2–4 weeks).[18] When it was decided to start OMZ, OIT was continued with the last dose that the patient tolerated. Dose increment was begun again 1 week after the first dose of OMZ. The time passed and the dose reached until initiation of OMZ treatment and the time passed during each phase of the OIT process were calculated. Any adverse events developed throughout the whole follow-up were recorded in detail.

Statistical Analyses

Statistical analyses were performed with the statistical software package IBM SPSS V24 (IBM Corp, NY, USA). The assumption of normality was tested via Shapiro–Wilk test. Nonnormally distributed continuous variables were reported as median (minimum–maximum) values while normally distributed variables were presented with mean ± SD values. The student *t*-test and Mann–Whitney U test were used to compare normally and nonnormally distributed continuous variables of two independent groups, respectively. Chi-square test was used to compare categorical variables between groups. Receiver operating characteristic (ROC) analysis was used for choosing the most appropriate cutoff value. *p* value less than 0.05 was considered statistically significant.

Results

Forty-one patients (27 boys and 14 girls) were started OIT at a median age of 5.1 (3.0–11.6) years. OIT was performed

Table 3 Demographic, clinical, and laboratory features of the patients.

(n = 41)	Feature
Gender, male, n (%)	27 (66)
Age at the onset of OIT (years) median (min-max)	5.1 (3.0-11.6)
Age at first symptom (months) median (min-max)	5.0 (1.0-6.0)
Frequency of symptoms before admission, n (%)	
Anaphylaxis	39 (95.1)
Urticaria/angioedema	37 (90.2)
Asthma	29 (70.7)
Atopic dermatitis	13 (31.7)
Allergic rhinitis	6 (14.6)
Proctocolitis/diarrhea	4 (9.8)
Total WBC count (/mm^3) mean ± SD (n = 39)	8562 ± 2544
AEC (/mm^3) median (min-max) (n = 39)	350 (0-1700)
Total IgE (kU/L) median (min-max)	374 (38-3250)
Cow's milk sIgE (kU/L) median (min-max) (n = 38)	87.8 (2.9-874.0)
Casein sIgE (kU/L) median (min-max) (n = 22)	43.9 (0.8-461.0)
Beta-lactoglobulin sIgE (kU/L) median (min-max) (n = 11)	20.6 (0.4-78.1)
Egg white sIgE (kU/L) median (min-max) (n = 6)	14.0 (2.3-27.1)
Food wheel size (mm) median (min-max)	11 (5-25)

AEC: absolute eosinophil count, WBC: white blood cell, sIgE: specific IgE

with milk in 35 (85.4%) patients, egg white in 3 (7.3%) patients, milk and egg white in 3 (7.3%) patients. Twenty-two (53.6%) of the patients had developed tolerance to one or more food other than the current allergen(s). The most frequent clinical finding was anaphylaxis which developed in 39 (95.1%) of the patients. Median total IgE was 374 (38-3250) kU/L; milk and egg white sIgE were 87.8 (2.9-874.0) and 14.0 (2.3-27.1) kU/L, respectively. The detailed data about demographic characteristics, clinical and laboratory findings of the patients are given in Table 3.

All patients other than two with a recent anaphylaxis history underwent OFC tests (36 with milk, 5 with egg white). Median cumulative reaction doses at milk and egg white OFC tests were 115 (1.5-1615) and 27.5 (27.5-1292.5) mg of protein, respectively. The initial doses for milk and egg OIT were 10 (0.15-66) and 5.5 (5.5-48.0 mg) of protein, respectively.

Twenty-one patients who achieved maintenance phase of OIT without OMZ formed the *OIT group*. Seventeen of the 18 patients who received OMZ reached maintenance phase and formed the *OIT + OMZ group*. A total of three patients from both groups had to stop treatment because of eosinophilic esophagitis (EoE) emerging in 13th-15th weeks of OIT. Patients who could reach maintenance phase (n = 38) constituted 93% of the whole group (desensitization rate). The summary scheme for design and results of the study is shown in Figure 1.

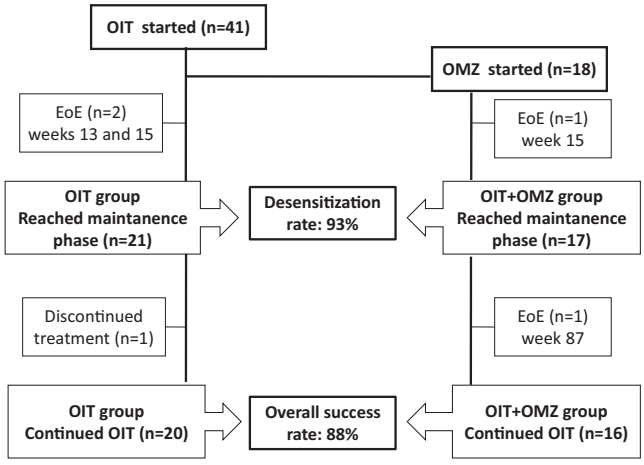

Figure 1 Summary scheme for design and results of the study.

OIT group (n = 21) and OIT + OMZ group (n = 17) were similar in means of clinical findings, demographic characteristics, and laboratory findings except total IgE (data not shown, p > 0.05). Median total IgE was higher in the OIT + OMZ group than in the OIT group (respectively: 454 (115-3250) and 265 (38-2560) kU/L, p = 0.023). Since the majority of the group consisted of milk OIT patients, subsequent statistics regarding doses were made on milk.

The median cumulative reaction dose during the milk OFC test and relevantly the milk OIT initial dose were lower in the OIT + OMZ group than in the OIT group (respectively 49.5 (1.5-815) vs. 115 (14.5-1615) mg, p = 0.037; 1.5 (0.15-33) vs. 10.0 (1.5-66) mg, p = 0.021) (Table 4).

The initial doses for 35 patients undergoing milk OIT who successfully reached the maintenance phase were assessed using ROC analysis. The cutoff value for predicting the need for OMZ during OIT was determined to be 2.5 mg, with a sensitivity of 78.9% and a specificity of 56.2% (p = 0.023, AUC = 0.725). The frequency of patients who started OIT with a dose lower than 2.5 mg was higher in the OIT + OMZ group compared to the OIT-only group (56.3% vs. 21.1%, p = 0.032). The ROC curve is shown in Figure 2.

The expected duration of the dose escalation phase, that is, the time between the initial and target doses in the absence of any pause, was solely dependent on the initial dose of OIT and was longer in the OIT + OMZ group than in the OIT group (p = 0.029). The real duration taken to reach the maintenance phase was also longer in the OIT + OMZ group than in the OIT group (p = 0.023) (Table 4).

Median AR rate in the OIT + OMZ group before starting OMZ was higher than the AR rate in the OIT group (0.67 vs. 0.11, p<0.001). After starting OMZ, median AR rate in the OIT + OMZ group declined to 0.00 (p<0.001) and was lower than the values of the OIT group (p<0.001). The comparison of groups in means of data about OFC test and OIT process is present in Table 4.

After reaching the maintenance phase, one patient from the OIT group left OIT voluntarily citing allergic side effects at the 79th week of OIT and did not come for further evaluation. Another patient from OIT + OMZ group left OIT due to EoE at the 87th week of OIT (Figure 1). EoE frequency in our study group was 9.7% (4/41) and similar

Table 4 Comparison of data about OFC test and OIT process.

	OIT group	OIT + OMZ group	p-value
Cumulative reaction dose in OFC (mg)[a] median (min-max)	115 (14.5-1615)	49.5 (1.5-815)	**0.037**
Starting dose of OIT (mg)[a] median (min-max)	10.00 (1.50-66)	1.50 (0.15-33)	**0.021**
Expected time to reach maintenance phase (wks) mean ± SD	18.6 ± 2.3	20.5 ± 2.6	**0.029**
Real time to reach maintenance phase (wks) mean ± SD	21.7 ± 4.6	25.6 ± 5.3	**0.023**
Allergic reaction rate-before OMZ median (min-max)	0.11 (0.00-0.50)[b]	0.67 (0.20-5.00)	<**0.001**
Allergic reaction rate-after OMZ median (min-max)	0.11 (0.00-0.50)[b]	0.00 (0.00-0.10) **p < 0.001**[c]	<**0.001**

[a]For milk only.
[b]In this group, OMZ was not used. So the same allergic reaction (AR) rate represented the whole OIT process.
[c]The p-value concerning the comparison of AR rates before and after OMZ in the OIT + OMZ group.

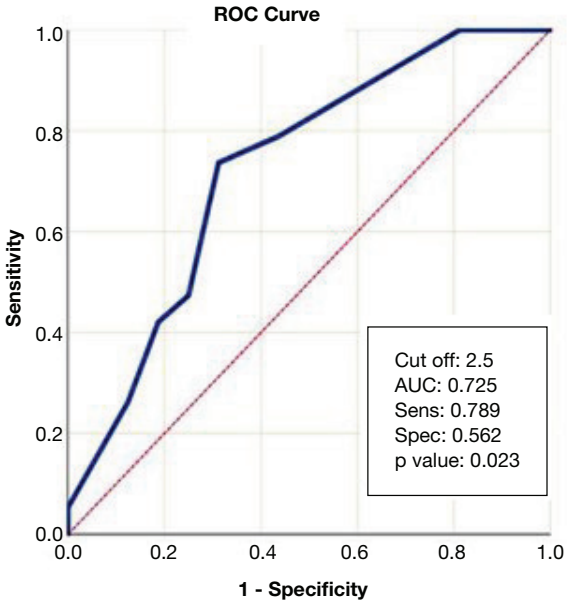

Figure 2 Receiver operating characteristic curve analysis for initial doses of milk oral immunotherapy (OIT) predicting the need for omalizumab during OIT.

between groups. Treatment attendance rate (overall success rate) was 87.8% (n = 36) in the whole study group. Median follow-up period of these patients continuing OIT was 191 (77-351) weeks and was similar between two groups (p = 0.66).

During follow-up, the presence, frequency, and severity of side effects were observed, and an attempt was made to gradually increase the OMZ application interval for each patient who did not experience any problems in this regard. Median number of OMZ injections was 6.5 (1-50). Excluding four patients who received only one or two doses of OMZ, median period of OMZ was calculated as 106.5 (14-330) weeks and mean OMZ injection interval was 5.6±1.8 (3.5-10) weeks. Thirteen patients were able to discontinue OMZ (81%), six before the maintenance phase, three at the early weeks of the maintenance phase, and another four after a few months in the maintenance phase. In these patients who could discontinue treatment, median number of OMZ injections was 5.5 (1-22) and median period of OMZ was 35 (14-113) weeks. Three patients were not able to discontinue OMZ, although the interval could be extended up to 6-12 weeks. If we take a closer look at a few patients, patient 1 was the first patient we had started OMZ. The family desired to get rid of allergy so much that they were very patient in the whole process. Even if they experienced many mild reactions during the maintenance period, they did not give up the treatment. But as the time passed and the interval of OMZ injections was lengthened, the patient experienced a few anaphylaxis after exercise. So they decreased the dose of milk protein up to 3000 mg. Patient 10 had taken only one dose of OMZ during the escalation phase (at 31st week) of OIT. We restarted OMZ when he had an anaphylaxis during the third month of maintenance phase and continued regularly at 8-12 week intervals thereafter. During follow-up, he could stop the treatment after eleven doses of OMZ. The detailed data about the OFC test and OIT process for each patient in the OMZ group was given in Table 5.

Discussion

In this study in which we retrospectively evaluated patients receiving food OIT, we determined that OMZ prevented treatment failure and compliance problems due to severe and frequent ARs. In addition, it was determined that patients who needed OMZ during OIT mostly had lower reaction thresholds during OFC than the OIT-only group.

In the 41 patients involved in this study, desensitization rate was 93%. The reason for failure to achieve maintenance in three patients from both groups was EoE, not IgE-mediated ARs. In a review of studies using OIT for different foods, partial and complete desensitization rates were reported to be between 57-100% and 29-90%, respectively.[1] In a study of milk OIT performed in patients with very severe ARs and high CM-sIgE levels as in our study group, only 36% of patients had complete desensitization.[3] If OMZ was not used in the patients with frequent and severe reactions in our study, complete desensitization rate would be similarly low.

In two previous randomized controlled trials, the OIT patients receiving OMZ had lower percentage of doses associated with adverse reactions when compared to OIT patients receiving placebo.[8,19] In our study, the AR rate was formulated to combine severity and frequency of ARs on a

Table 5 The detailed data about the OFC test and OIT process for the OMZ group.

		OFC	OIT- Escalation phase					OIT – Maintenance phase		Total	
				Before/After OMZ							
Pt(Sex)	Food	Rxn step	Initial dose (mg)	Dose (mg)	Time (weeks)	AR (nb)	Total time (wks)	During OMZ time (wks)	After OMZ time (wks)	OMZ time (wks)/ shots (nb)	follow-up time (wks)
1(F)*	Milk	3	1.5	100/6600[a]	21/16	7/1	37	314	-	330/50	351
2(F)	Milk	1	0.15	10/6600	6/22	2/0	28	59[b]	-	81/17	87
3(M)	Milk	9	33	400/6600	16/14	6/0	30	99	207	113/22	336
4(F)	Milk	3	1.5	1650/6600	18/8	6/0	26	102	207	110/21	335
5(M)	Milk	1	0.15	0.15/1320	1/14	1/[b]	-	-	-	14/4	15
6(M)	Milk	3	1.5	3/6600	2/23	1/0	25	12	223-266	35/7	303
7(M)	Milk	6	10	330/6600	10/18	2/0	28	85	90-133	103/19	246
8(F)*	Milk	3	1.5	10/6600	2/21	2/1	23	200	-	221/39	223
9(M)	Egg	1	5.5	145/4950	6/13	7/1	19	-	194	13/2	213
10(M)	Milk	4	1.5	4125/6600	31/4	5/0	35	110[c]	29	4/1&110/11	191
11(M)*	Milk	-	0.15	2/6600	4/22	20/2	26	90-133	-	155/20	159
	Egg		5.5	24/4950	4/16		20				
12(F)	Milk	-	0.15	0.15/6600	2/25	10/2	27	-	130	25/5	157
13(M)	Milk	5	3	3300/6600	13/4	3/0	17	-	142	4/1	159
14(M)	Milk	9	33	3300/6600	15/6	1/0	21	-	92	6/2	113
15(M)	Milk	7	20	50/6600	4/21	1/1	25	6	51	27/6	82
16(M)	Milk	3	1.5	100/6600	8/20	2/0	28	-	82	19/5	110
17(F)	Milk	5	3	330/6600	9/12	3/0	21	2	89	14/4	112
	Egg	2	12.1	176/4950	9/17		26				
18(M)	Milk	8	30	500/6600	10/10	3/1	20	-	98	4/1	118

*Three patients continue to receive OMZ.
[a]During follow-up, reduced the dose to 75–100 mL (2500–3000 mg) since symptoms were experienced during exercise.
[b]Nausea, vomiting, stomachache. Eosinophilic esophagitis in biopsy.
[c]There is a 17-week period during maintenance before reinitiation of OMZ.
AR: allergic reaction, F: female, M: male, nb: number, wks: weeks.

time basis. To the best of our knowledge, this is the first study that compared the ARs of the same patient group before and after the OMZ treatment. The higher AR rate in the OIT + OMZ group declined sharply after starting OMZ to values lower than the OIT group. Actually, it was this difference in the frequency and severity of ARs that had led us to start OMZ in those patients. That is, this result was just the declaration of the known. The primary aim of the study was to find determinants to predict this need for OMZ before severe side effects occur. Thus, time would have been saved while eliminating the risk of fatal ARs. But clinical findings, demographic characteristics, and laboratory parameters about allergic sensitization did not provide clues in this regard. Although groups were different in means of median total IgE levels, each group had values in a broad range. So a certain IgE value did not point out the OMZ necessity during OIT.

The two groups differed only in means of OFC tests and OIT process. Patients in the OIT + OMZ group reacted in earlier steps of the OFC test although the mechanism for low reaction threshold is unknown. In a recent study, the patients who developed anaphylaxis after accidental intake or showed systemic reactions with minimal doses (not specified) during OFC were considered as refractory to conventional OIT and OMZ was started before OIT.[20] In this study, OMZ was started when patients really failed conventional OIT. The cutoff value for initial doses of milk OIT predicting the need for OMZ during OIT was determined to be 2.5 mg, although the specificity is not so high. Therefore, it may be an option for safety to start OMZ before the first dose of OIT in patients who react in the first four steps of OFC. However, it would be sensible to wait and see whether OMZ will be needed in the rest of the patients, given that many patients were able to complete OIT without this costly treatment.

In the previous studies combining OMZ with OIT, OMZ was started 8–16 weeks before OIT.[7–9,19] Pharmacokinetically, OMZ is absorbed slowly after subcutaneous administration and reaches the peak serum concentration after 7–8 days.[18] Based on this information, we did not interrupt OIT when we decided to start OMZ, unlike the above studies, but continued with the last week's dose. This practice did not lead to a negative situation regarding drug efficacy as evidenced by the rapid reduction in the rate of ARs. It has also contributed to the cost of treatment, via reducing the number of doses given.

Although there is no consensus on when to stop OMZ as in when to start, there are some studies in which the drug is discontinued after certain periods of use. Nadeau et al. used OMZ in 11 patients until maintenance phase and did not experience an AR due to discontinuation of treatment.[9] Martorell-Calatayud et al. started OMZ 8 weeks before reintroduction of OIT in 14 patients resistant to conventional OIT. Two months after reaching the maintenance

phase, they discontinued OMZ. Anaphylactic reactions developed in three of the patients 2–4 months after stopping OMZ (21%).[7] The latter study had a similar population to our OIT + OMZ group with regard to resistance to conventional OIT. Similarly in a real-life survey from Spain, 36% of patients taking OIT for severe cow's milk allergy developed anaphylactic reactions after discontinuation of OMZ (after a median use of 7.5 months). Sudden interruption caused anaphylaxis more frequently than progressive discontinuation (50% vs. 12.5%).[21] Therefore, in our study, we cautiously preferred to extend the OMZ intervals instead of stopping the drug abruptly in order to avoid severe ARs. Decisions on continuation or discontinuation and interval extension of OMZ were taken based on patients by observing side effects. The OMZ usage period was quite variable in different patients ranging between 14 weeks and 6 years. The patients who were able to discontinue OMZ were in the majority (81%) and the longest period of OMZ in this group was 2 years.

This study had some limitations. First, it was a retrospective study and most of the data were based on patient records. But this limitation was minimized by the fact that all patients were followed closely by the same physician team and the records were quite detailed. Second, the study population was not large, which was a natural result of the rarity of food allergic patients receiving OIT and OMZ at the present time. On the other hand, the real-life data it provided about the use of OMZ in patients during OIT is the strength of this study.

Conclusion

OMZ decreases the frequency and severity of IgE-mediated ARs during OIT. Patients who had OMZ requirement during OIT had a low reaction threshold starting with the OFC test and continuing throughout the OIT process. The lack of laboratory parameters predicting this low threshold makes it necessary to do OFC. Very low reaction doses in the OFC may be a clue about the OMZ requirement. Given the high cost of OMZ, it seems reasonable to start the OIT process carefully and reserve OMZ for patients with serious and frequent side effects. Lastly, we may recommend that the drug be discontinued gradually by extending the interval rather than abruptly in order to avoid severe reactions.

Acknowledgments

The authors would like to thank Su Özgür and Tuba Tuncel for statistical and editorial support, respectively.

References

1. Begin P, Chinthrajah RS, Nadeau KC. Oral immunotherapy for the treatment of food allergy. Human vaccines & immunotherapeutics. 2014;10(8):2295–302. https://doi.org/10.4161/hv.29233
2. Clark AT, Ewan PW. Food allergy in childhood. Arch Dis Child. 2003;88(1):79–81. https://doi.org/10.1136/adc.88.1.79
3. Longo G, Barbi E, Berti I, Meneghetti R, Pittalis A, Ronfani L, et al. Specific oral tolerance induction in children with very severe cow's milk-induced reactions. J. Allergy Clin. Immunol. 2008;121(2):343–47. https://doi.org/10.1016/j.jaci.2007.10.029
4. Navinés-Ferrer A, Serrano-Candelas E, Molina-Molina GJ, Martín M. IgE-Related Chronic Diseases and Anti-IgE-Based Treatments. J Immunol Res. 2016;2016:8163803. https://doi.org/10.1155/2016/8163803
5. Dantzer JA, Wood RA. Anti-immunoglobulin E for food allergy. Ann Allergy Asthma Immunol. 2023;131(1):11–22. https://doi.org/10.1016/j.anai.2023.03.030
6. Yu L, Zhang H, Pan J, Ye L. Pediatric usage of Omalizumab: A promising one. World Allergy Organ J. 2021;14(12):100614. https://doi.org/10.1016/j.waojou.2021.100614
7. Martorell-Calatayud C, Michavila-Gómez A, Martorell-Aragonés A, Molini-Menchón N, Cerdá-Mir JC, Félix-Toledo R, et al. Anti-IgE-assisted desensitization to egg and cow's milk in patients refractory to conventional oral immunotherapy. Pediatric allergy and immunology: official publication of the European Society of Pediatric Allergy and Immunol. 2016;27(5):544–46. https://doi.org/10.1111/pai.12567
8. Wood RA, Kim JS, Lindblad R, Nadeau K, Henning AK, Dawson P, et al. A randomized, double-blind, placebo-controlled study of omalizumab combined with oral immunotherapy for the treatment of cow's milk allergy. J. Allergy Clin. Immunol. 2016;137(4):1103–10.e11. https://doi.org/10.1016/j.jaci.2015.10.005
9. Nadeau KC, Schneider LC, Hoyte L, Borras I, Umetsu DT. Rapid oral desensitization in combination with omalizumab therapy in patients with cow's milk allergy. J. Allergy Clin. Immunol. 2011;127(6):1622–4. https://doi.org/10.1016/j.jaci.2011.04.009
10. Takahashi M, Soejima K, Taniuchi S, et al. Oral immunotherapy combined with omalizumab for high-risk cow's milk allergy: a randomized controlled trial. Sci. Rep. 2017;7:17453. https://doi.org/10.1038/s41598-017-16730-6
11. Azzano P, Paquin M, Langlois A, Morin C, Parizeault G, Lacombe-Barrios J, et al. Determinants of omalizumab dose-related efficacy in oral immunotherapy: Evidence from a cohort of 181 patients. J. Allergy Clin. Immunol. 2021;147(1):233–43. https://doi.org/10.1016/j.jaci.2020.08.039
12. Kawakami T, Blank U. From IgE to Omalizumab. Journal of immunology (Baltimore, Md: 1950). 2016;197(11):4187–192. https://doi.org/10.4049/jimmunol.1601476
13. Pajno GB, Fernandez-Rivas M, Arasi S, Roberts G, Akdis CA, Alvaro-Lozano M, et al. EAACI Guidelines on allergen immunotherapy: IgE-mediated food allergy. Allergy. 2018;73(4):799´815. https://doi.org/10.1111/all.13319
14. Dello Iacono I, Tripodi S, Calvani M, Panetta V, Verga MC, Miceli Sopo S. Specific oral tolerance induction with raw hen's egg in children with very severe egg allergy: a randomized controlled trial. Pediatric allergy and immunology: official publication of the European Society of Pediatric Allergy and Immunol. 2013;24(1):66–74. https://doi.org/10.1111/j.1399-3038.2012.01349.x
15. Duman Senol H, Topyildiz E, Ulusoy Severcan E, Eren Akercan S, Cigerci Gunaydin N, Gulen F, et al. Could Age and Oral Challenge Outcomes Identify High-Risk Patients During Cow's Milk Oral Immunotherapy? Pediatric Allergy, Immunol, and Pulmonol. 2022;35(2):95–101. https://doi.org/10.1089/ped.2022.0003
16. Jagdis A, Berlin N, Barron C, Giruparajah M, Leader N, Maclachlan S, et al. Effect of ketotifen premedication on adverse reactions during peanut oral immunotherapy. Allergy, asthma, and clinical immunology: official journal of the Canadian Society of Allergy and Clin. Immunol. 2014;10(1):36. https://doi.org/10.1186/1710-1492-10-36

17. Asaumi T, Ebisawa M. How to manage food dependent exercise induced anaphylaxis (FDEIA). Current opinion in allergy and clinical immunology. 2018;18(3):243–7. https://doi.org/10.1097/ACI.0000000000000442
18. Xolair® (Omalizumab). Prescribing Information for US Healthcare Professionals (Revised: 08/2023). ©2023 Genentech USA, Inc. and Novartis Pharmaceuticals Corporation. https://www.xolair.com/
19. Andorf S, Purington N, Block WM, Long AJ, Tupa D, Brittain E, et al. Anti-IgE treatment with oral immunotherapy in multifood allergic participants: a double-blind, randomised, controlled trial. Lancet Gastroenterol & Hepatol. 2018;3(2):85–94. https://doi.org/10.1016/S2468-1253(17)30392-8
20. Ayats-Vidal R, Riera-Rubió S, Valdesoiro-Navarrete L, García-González M, Larramona-Carrera H, Cruz OA, et al. Long-term outcome of omalizumab-assisted desensitisation to cow's milk and eggs in patients refractory to conventional oral immunotherapy: real-life study. Allergol Immunopathol. 2022;50(3):1–7. https://doi.org/10.15586/aei.v50i3.537
21. Ibáñez-Sandín MD, Escudero C, Candón Morillo R, Lasa EM, Marchán-Martín E, Sánchez-García S, et al. Oral immunotherapy in severe cow's milk allergic patients treated with omalizumab: Real life survey from a Spanish registry. Pediatric allergy and immunology: official publication of the European Society of Pediatric Allergy and Immunology. 2021;32(6):1287–95. https://doi.org/10.1111/pai.13517