LETTER TO THE EDITOR

Anti-IgE-assisted desensitization to egg and cow's milk in patients refractory to conventional oral immunotherapy

To the Editor:

Oral immunotherapy (OIT) is a significant focus of treatment for egg and cow's milk food allergy, inducing desensitization in the majority of individuals with these sensitivities (1, 2). A major drawback of OIT is the frequency of adverse effects, and although most are mild and self-limited, the use of parenteral epinephrine is not infrequent. As many as 20–30% of food-allergic patients are refractory to desensitization, particularly patients with higher initial food-specific IgE levels (3).

To address some of the safety issues associated with OIT, anti-IgE monoclonal antibody (omalizumab) was proposed as an adjunct to facilitate OIT by reducing OIT-induced allergic reactions. Open-label pilot studies have demonstrated efficacy of omalizumab as an adjunctive therapy with OIT in children with milk allergy, in high-risk peanut-allergic patients and in simultaneous desensitization to multiple food allergens (4–6).

Additional support for the effectiveness of omalizumab-facilitated OIT comes from a randomized, double-blind, placebo-controlled trial of omalizumab combined with OIT in the treatment of cow's milk allergy. In this trial, omalizumab significantly reduced dose-related symptoms and OIT-related side effects, including a reduction in treatments with epinephrine (7). Evolution after discontinuation of omalizumab, however, remains to be thoroughly studied.

We report our experience with a protocol of omalizumab-assisted OIT and the evolution during 12 months after discontinuation of omalizumab therapy in 14 egg- and cow's milk-allergic patients refractory to conventional OIT (Table 1). These patients were unable to tolerate conventional OIT because of allergic reactions, exhibiting grade 3-4 anaphylactic symptoms (Clark and Ewan grading (8)).

Omalizumab as an off-label indication was dosed according to the package insert. All patients/parents provided informed consent. Nine weeks after the start of omalizumab treatment, we performed the desensitization procedure again. Cow's milk OIT followed the protocol previously described by Martorell et al. (9) (initial dose, 0.33 mg of cow's milk protein; final dose, 6.6 g). In the maintenance phase, children continued drinking 200 ml of cow's milk (6.6 g of protein) once a day, every day, and consumed cow's milk and dairy products without restrictions. Patients followed the same treatment plan for egg-OIT with pasteurized liquid raw egg white (initial dose, 0.06 mg of hen's egg (HE) protein; final dose, 1.8 g). A dose of 1.8 g (17 ml) of liquid raw egg white is roughly equivalent to 1/2 HE (Clara Guillen, Valencia, Spain, whose allergenicity is equivalent to raw egg white (EW)). The induction phase lasted 18 weeks and started with a 2-day in-hospital rush phase in which patients received increasing doses hourly (first day: 1/100 dilution with water: 0.05 ml (0.06 mg EW protein), doubling doses up to 0.8 ml; second day: 0.8 ml 1/100, doubling doses up to 1.2 ml 1/10). Upon discharge, patients continued the last tolerated dose once daily for a week. Thereafter, outpatient clinic staff administered weekly increases up to the dose of 17 ml.

Hospital staff supervised all dose increases, which patients subsequently maintained at home (cow's milk twice a day and egg white once a day), with increases once a week. Patients received no premedication.

One week after the end of the desensitization procedure, patients underwent an open food challenge (total dose: 33 ml pasteurized EW, around 1 HE). In the maintenance phase, children continued having 17 ml of pasteurized raw EW three times a week without interruption, along with unrestricted access to any food containing egg.

Patients received omalizumab for 2 months after reaching the final dose of the induction phase and then it was discontinued.

In the absence of previous experience, our great concern was the possible reduction in clinical tolerance with suspension of omalizumab. Because discontinuation of omalizumab can reduce clinical threshold reactivity, a month after suspending omalizumab we reintroduced desensitization with 25% of the maintenance dose (initial dose: 50 ml of CM and 5 ml of EW). All patients reached the maximum dose again and began maintenance with daily 200 ml of CM and 17 ml of EW, with

Table 1 Subjects' demographics at enrollment

Subject no	Age	Anaphylaxis with prior exposure*	Comorbidity: asthma	OIT
1	11 y	Yes	Yes	CM
2	3 y-11 mo	Yes	Yes	CM
3	6 y	Yes	Yes	CM
4	3 y-6 mo	Yes	Yes	CM
5	3 y	Yes	Yes	CM
6	5 y-9 mo	Yes	Yes	EW
7	8 y-8 mo	No	Yes	EW
8	9 y-4 mo	Yes	No	EW
9	7 y	Yes	No	EW
10	5 y-3 mo	Yes	Yes	EW
11	13 y	No	Yes	EW
12	5 y	Yes	Yes	EW
13	5 y-11 mo	No	No	EW
14	6 y	Yes	No	EW

*Symptoms with egg or cow's milk based on subject-reported histories or symptoms during in-office challenge.
EW: egg white, CM: cow's milk.

Abbreviations:
OIT, oral immunotherapy; HE, hen's egg; EW, egg white; CM, cow milk.

Table 2 Individual IgE levels (kU/L) over time (baseline and 12 months after OMZ)

Subject no.	Baseline CM	12 mo CM	Baseline CS	12 mo CS	Subject no.	Baseline EW	12 mo EW	Baseline OVM	12 mo OVM
1	101.00	24.90	101.00	20.00	6	30.30	6.12	32.20	6.85
2	101.00	32.30	84.00	27.40	7	101.00	14.10	101.00	19.30
3	101.00	35.40	101.00	41.80	8	15.50	3.10	48.60	8.69
4	45.00	3.99	37.40	3.91	9	8.00	1.06	9.31	1.14
5	47.20	5.22	38.90	4.88	10	17.50	4.98	11.10	2.72
					11	8.03	0.99	10.60	1.18
					12	101.00	DO	101.00	DO
					13	44.00	2.94	65.20	6.17
					14	4.70	1.03	4.88	1.14

CM: cow's milk, CS:casein, EW: egg white, OVM: ovomucoid, DO: dropped out.

monitoring for 12 months after discontinuation of omalizumab therapy.

At the end of induction phase, all patients (100%) had achieved complete desensitization. All the egg-allergic patients passed the challenge with 33 ml of raw EW after completing the induction phase.

In terms of safety, only 4 patients (28%) developed mild allergic reactions during the induction phase of OIT. Subject 2 reacted at the 0.3 ml dose (rhinitis, cough), 8 ml dose (rhinitis), and 25 ml dose of CM (ear pruritus). Subject 4 reacted at the 100 ml dose (rhinitis, urticaria around the mouth) and 150 ml dose of CM (cough, urticaria around the mouth). Subject 7 reacted to some doses of EW with abdominal pain and conjunctivitis and has not required specific therapy. Subject 14 reacted at the 2 ml dose of EW with rhinitis and urticaria. None required epinephrine.

During the 12-month maintenance period, there were no adverse reactions after discontinuation of omalizumab in 2 patients on CM-OIT and 4 patients on EW-OIT; 2 patients on EW-OIT experienced abdominal pain and rhinitis or mouth pruritus at some doses that have not altered the maintenance therapy. All 8 patients passed the final challenge with 200 ml of CM or 33 ml of EW at the end of follow-up.

Nevertheless, 6 patients (patients 1, 4, 5, 10, 12, and 14), at 2.5–4 months after discontinuing omalizumab (1: 3.5 months; 4: 2.5 months; 5: 2.5 months; 10: 4 months; 12: 2.5 months; 14: 3 months), developed grade 3–4 anaphylactic symptoms (1: abdominal pain, vomiting, bronchospasm, urticaria, outer ear angioedema. 4: rhinitis urticaria, cough, bronchospasm. 5: urticaria, cough, angioedema, vomiting. 10: rhinitis, abdominal pain, vomiting. 12: urticaria, bronchospasm. 14: urticaria, abdominal pain, vomiting) with a decrease in the threshold dose eliciting allergic reactions. The tolerated maintenance dose at the end of 12 months of follow-up was 100 ml of cow's milk in Patient 1, 50 ml in Patient 4, and 100 ml in Patient 5; 5 ml of egg white in Patient 10, and 10 ml in Patient 14, with one subject having dropped out (Patient 12).

Patients 1, 4, and 5 resumed omalizumab, and 6 months later, they are on maintenance therapy with 200 ml of CM and taking dairy products without restrictions.

The association with omalizumab seems to solve the problem of the safety of the OIT and minimize adverse reactions during the desensitization process, as observed by Nadeau (2) and Kim (8).

Despite suggestions that association with omalizumab can reduce the time to achieve maintenance dosing, our desensitization protocol seems to be safer than rapid oral desensitization (5).

The question arises of when to suspend omalizumab. The increase in the tolerable amount of food could be due, at least partially, to the direct effect of the omalizumab and not to the desensitization procedure. In addition, the IgE/anti-IgE complexes may trap incoming allergens and this capture can contribute to reducing the effective desensitization dose. Lafuente et al. report three cases of children with successful anti-IgE-assisted desensitization to egg who experienced reactions after discontinuation of omalizumab (10). As in our patients, allergic reactions occurred at 3-4 months after discontinuing omalizumab.

In previous studies, the ingestion of food continued with no or minor tolerable symptoms after stopping omalizumab (5–7). One possible reason for relapse in our patients and the Lafuente patients is that they were selected based on resistance to non-assisted omalizumab. We could probably consider these patients more sensitive than children typically included in other studies and thus more prone to relapse after stopping medication.

Lafuente et al. suggested that the allergenic food might be significant and that desensitization with CM is better tolerated than with egg (10). Nevertheless, in our series 60% of patients with CM-OIT and 33% of patients with EW-OIT relapsed after omalizumab suspension. The relapse ratio is probably less in EW-OIT because EW-allergic patients have lower levels of specific IgE than those allergic to cow's milk (Mann–Whitney U-test, p:0.035). We used raw pasteurized egg white for the EW-OIT maintenance treatment; however, Lafuente et al. used cooked egg for maintenance, which allergic children often reject and which could diminish the effectiveness of the maintenance treatment (10).

Twelve months after discontinuation of omalizumab, there was a statistically significant reduction in specific IgE levels for CM, casein, EW, and ovomucoid (Table 2) (Wilcoxon's test, $p < 0.05$), with no significant differences between those who relapsed and those who did not (Mann–Whitney U-test,

$p > 0.05$). We are unable to identify risk factors in patients who relapse.

Association of omalizumab allows safe and effective desensitization treatment in patients who have been refractory to it. Nevertheless, a percentage of patients relapse with decrease in the clinical reactivity threshold at 2–4 months after suspending omalizumab, suggesting the need for longer maintenance therapy with omalizumab.

Safer OIT would allow OIT to become widely available to patients with food allergy and association with omalizumab could be the key to opening that door.

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