The use of adjunctive therapies during oral immunotherapy: A focus on biologics

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ABSTRACT

Oral immunotherapy (OIT), thus far, is the most evaluated therapeutic approach for food allergy. However, OIT is not known to lead to a cure, and it carries a risk for allergic reactions. Adjunct therapies to OIT are currently being investigated to evaluate their effect on safety and outcome. Of these therapies, omalizumab is the most evaluated biologic. There is mounting evidence that omalizumab is effective in inducing rapid desensitization of OIT in both single-food and multiallergen OIT, while diminishing the rate of adverse reactions. Evaluation of other adjunct biologics, such as dupilumab and bacterial therapy, is underway.

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Food allergy is a significant public health problem, which affects 6% of children and up to 11% of adults.[1] Up until early 2020, the standard of care for food allergy consisted of strict avoidance of the food allergens and in keeping rescue medications available for emergency use. In January 2020, AR101 (Palforzia, Aimmune, Brisbane, California, USA) was granted U.S. Food and Drug Administration approval as an oral immunotherapy (OIT) treatment for peanut allergy.[2,3] OIT, in general, is the most investigated therapeutic approach for food allergy.[4] However, there has been significant heterogeneity among the studies, with variability that includes but not limited to type of food used, inclusion-exclusion criteria of patients, updosing protocol, maintenance target dose, and frequency of administration.[5] Nevertheless, although OIT is not known to lead to a cure, the majority of patients successfully achieve desensitization.[5]

Adjunctive therapies are currently being investigated in combination with OIT to evaluate whether these therapies can improve OIT's safety and efficacy. In this review, we discussed the use of these therapies, while focusing specifically on biologics. The U.S. Food and Drug Administration defines biologics as "products that include a wide range of products, such as vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins. They are isolated from a variety of natural sources, human, animal, or microorganism, and may be produced by biotechnology methods and other cutting-edge technologies."[6]

DISCUSSION

Anti–Immunoglobulin E Therapy

Omalizumab is a humanized mouse monoclonal anti–immunoglobulin E (IgE) antibody that binds to free serum IgE and decreases its availability to bind to FcεR1 receptors on the surface of the mast cells and basophils, which prevents their crosslinking and subsequent activation of the allergic cascade.[7] Omalizumab monotherapy was shown to increase the threshold dose of reactivity to peanut during oral food challenge (OFC).[8] Subsequently, in an attempt to increase the safety and efficacy of OIT, omalizumab was evaluated in a number of studies as an adjunct therapy.[9–11] Nadeau *et al.*[9] reported on the first pilot phase I study that investigated omalizumab use in combination with cow's milk OIT. Study subjects received omalizumab pretreatment for 9 weeks, followed by 7–11 weeks of milk OIT updosing; omalizumab was stopped at week 16.[9] Nine of 11 study participants (82%) tolerated the maintenance goal of 2000 mg.[9] One subject discontinued the study voluntarily due to abdominal migraine and

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another patient reached the dose of 1200 mg only after reacting to the 1000-mg dose and requiring epinephrine therapy.[9] Although no entry OFC was performed, the results of this pilot study, nevertheless, suggest that anti-IgE therapy facilitates rapid OIT updosing.[9]

In a subsequent open-label study that used a similar protocol, we evaluated omalizumab as an adjunct therapy to peanut OIT.[10] Thirteen patients, ages 8–16 years, with a high median peanut IgE value, of 229 KU/L, who reacted to ≤ 50 mg of peanut protein during entry OFC, which thus highlights their high sensitivity, received omalizumab monotherapy every 2–4 weeks for 12 weeks, followed by rapid escalation to 250 mg of peanut protein over a few hours (cumulative dose of 496 mg). A similar dose of 240 mg is typically achieved after 18 weeks of therapy by using Palforzia's or other similar protocols.[2,12] The patients then underwent rapid weekly updosing to 2000 mg of peanut protein over a median period of 8 weeks, after which omalizumab therapy was discontinued (Fig. 1).[10] This dose is reached at ~37–38 weeks of therapy by using conventional OIT protocols.[12,13] Twelve of 13 patients (92%) were successfully desensitized and tolerated 4000 mg of peanut protein during OFC on week 32, whereas one patient developed symptoms suggestive of eosinophilic esophagitis and was withdrawn from the study.[10] Adverse events were only noted in 2% of the doses, and the vast majority (97%) were mild to moderate (Table 1).[10]

In a subsequent multi-site, phase II, randomized, double-blind, placebo controlled trial, we further demonstrated omalizumab's utility in achieving a faster OIT desensitization.[11] Thirty-seven participants received omalizumab or placebo (3.5:1) for 12 weeks before and continued anti-IgE therapy for another 8 weeks after the initiation of peanut OIT.[11] The majority of the patients in the omalizumab group (79%) were able tolerate 2000 mg of peanut protein 6 weeks after stopping the study drug compared with only 12% of those in the placebo group.[11] There was no difference in adverse event frequency between the two groups, although the patients treated with omalizumab ingested much higher doses of peanut OIT compared with those who received placebo because the vast majority of the latter group could not tolerate rapid updosing (Table 1).[11]

Wood *et al.*[14] conducted a double-blind placebo controlled trial by using milk OIT combined with omalizumab. Fifty-seven participants received omalizumab or placebo (1:1) for 4 months, followed by an open-label milk OIT for 24 months. Although, there was no significant difference in efficacy (89% of the omalizumab group tolerated 10,000 mg of milk protein during OFC compared with 71% of the placebo arm) versus sustained unresponsiveness (48% versus 36%), the omalizumab-treated group had significantly fewer adverse reactions to OIT during escalation: these occurred in 2.1% of doses/subject in the

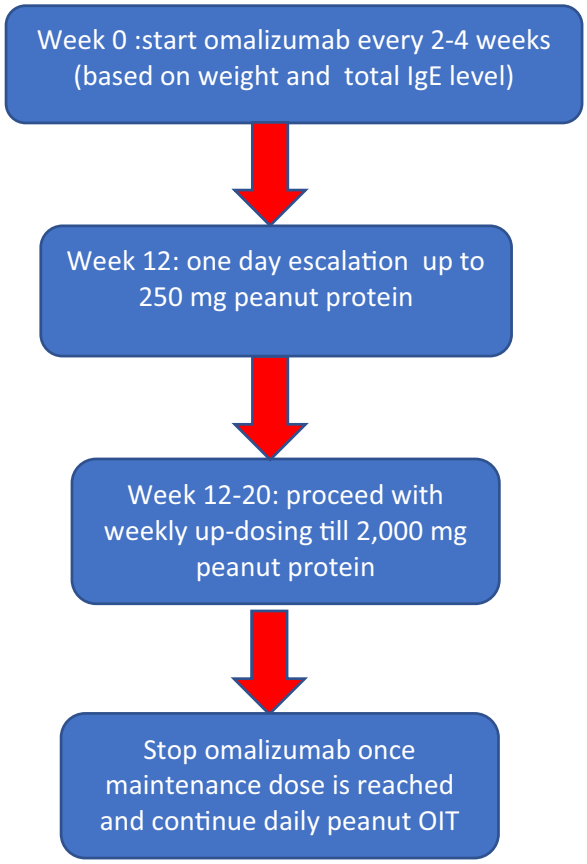

Figure 1. *Suggested omalizuma and /peanut OIT desensitization protocol up to 2000 mg of peanut protein (based on Ref. 10); omalizumab is not U.S. Food and Drug Administration approved yet for food allergy treatment.*

omalizumab arm compared with 16% of doses/patient in the placebo arm ($p = 0.0005$).[14] There also was a significant difference in dose-related reactions that required treatment (0.0% in omalizumab group versus 3.8% in placebo group; $p = 0.0008$).[14] In addition, updosing was faster in the omalizumab group compared with placebo (198 doses in the omalizumab group versus 225 doses in the placebo group; $p = 0.008$).[14]

Similarly, in multi-allergen food OIT studies, omalizumab was shown to be effective in facilitating rapid desensitization.[12,15,16] An initial safety trial that used OIT for multiple food allergens showed that a 250-mg allergen protein dose (1250 mg cumulative for five different foods) could be administered after only 9 weeks of omalizumab pretreatment, in 76% of the subjects who were treated.[12] In a randomized, double-blind, placebo controlled trial, the patients received either omalizumab or placebo for 16 weeks, with multifood OIT for up to five foods initiated at week 8.[15] At week 36, 83% of the patients who received omalizumab passed OFC up to 2000 mg of protein to two or more foods compared with 33% of those who received

Table 1 **Comparison of the efficacy and adverse events outcomes between studies of OIT alone and OIT with omalizumab**

Study	Characteristics of Study Subjects, OIT; *N*; ages (y)	Methods and Efficacy Outcome	Adverse Events Outcome
OIT as stand-alone therapy PALISADE Group of Clinical Investigators *et al.*,[2] 2018	Peanut; 496; 4–17	67.2% of the active treatment group tolerated ≥ 600 mg of peanut protein without dose-limiting symptoms at the exit food challenge (after 24 wk of a 300-mg daily maintenance dose) compared with 4% of the placebo group	4.3% of the active treatment group reported severe reactions compared with 0.8% of the placebo group
OIT with omalizumab (rapid desensitization) Schneider *et al.*,[10] 2013	Peanut; 13; 8–16	The study subjects were pretreated with omalizumab for 12 wk and 8 wk after initiation of peanut OIT; at wk 12, the study subjects underwent rapid 1-day desensitization up to 250 mg of peanut protein; escalation up to 2000 mg of peanut protein over 8 wk; 12 of 13 patients (92%) tolerated 4000 mg of peanut protein on wk 32	2% of the total doses (97% were mild-to-moderate reactions)
MacGinnitie *et al.*,[11] 2017	Peanut; 37; 6–19	The study subjects were pretreated with omalizumab vs placebo for up to 12 wk and 8 wk after initiation of peanut OIT; at wk 12, the study subjects underwent rapid 1-day desensitization up to 250 mg of peanut protein; 79% tolerated 2000 mg of peanut protein compared with 12% of the placebo group 6 wk after stopping omalizumab	Overall, reactions occurred after 7.8% of OIT doses administered in the omalizumab arm vs 16.8% in the placebo arm, despite subjects treated with omalizumab receiving higher doses of peanut; this difference was not statistically significant
OIT with omalizumab (slow desensitization) Wood *et al.*,14 2016	Milk; 57; 7–32	The study subjects were pretreated with omalizumab vs placebo for 4 mo, followed by open milk OIT for 24 mo; the efficacy between the omalizumab vs the placebo group was not significantly different	The omalizumab-treated group had significantly fewer adverse reactions to OIT during escalation (2.1% of doses/subject in the omalizumab arm compared with 16% in the placebo arm, $p = 0.0005$); dose-related reactions that required treatment were significantly less in the omalizumab group (0.0%) compared with placebo (3.8%; $p = 0.0008$); updosing was faster in the

Table 1 **Continued**

Study	Characteristics of Study Subjects, OIT; *N*; ages (y)	Methods and Efficacy Outcome	Adverse Events Outcome
			omalizumab group compared with the placebo group (198 doses in the omalizumab group vs 225 doses in the placebo group; $p = 0.008$)
Multifood OIT with omalizumab (rapid desensitization) Andorf *et al.*,[15] 2018	Multifood; 48; 4–15	The study subjects were pretreated with omalizumab vs placebo for 16 wk; they were initiated on multifood OIT (2–5 foods) on wk 8; at wk 36, 83% of the patients who received omalizumab passed OFC up to 2000 mg of protein to two or more foods compared with 33% of those who received placebo; significantly shorter times to reach maintenance dosing of 2000 mg of each food were achieved in omalizumab vs placebo (as early as 12 vs 20 wk; $p = 0{\cdot}001$)	The rate of adverse events while on the study drug was lower in the omalizumab group (27%) compared with the placebo group (68%; $p = 0.008$)

OIT = Oral immunotherapy.

placebo. The rate of adverse events was lower while being treated with omalizumab (27%) compared with those who received placebo (68%; $p = 0.008$), although it was similar between the two groups after omalizumab was stopped.[15]

As reviewed above, when used with OIT, omalizumab therapy is ultimately discontinued, typically after maintenance therapy is reached. Long-term studies that evaluated this approach, however, are scarce and have led to conflicting data. In one of the longest follow-up studies, which spanned 72 months of therapy and up to 67 months of maintenance, only 7 of the 13 initially enrolled patients (54%) continued on peanut OIT.[17] Hence, although omalizumab allowed for faster and effective desensitization in these sensitive patients, with a median serum peanut IgE level among the highest reported in peanut OIT literature, 46% discontinued therapy primarily because of allergic reactions, which suggests that longer omalizumab therapy may be beneficial.[17] The patients who stopped therapy had higher 12-month peanut-IgE and Arah2-IgE levels compared with those who did not stop therapy. It is possible that such patients might benefit from longer omalizumab administration. However, in another long-term follow-up study, which evaluated patients who underwent OIT to up to eight different foods with or without omalizumab pretreatment and were maintained on either a high (2000–4000 mg) or a low dose of food protein (median, 300 mg), there was no reported anaphylaxis for up to 62 months of maintenance therapy.[18]

To determine the effective dose of omalizumab combined with OIT, Azzano *et al.*[19] reported on a cohort of 181 patients who received multifood OIT for up to six foods after being pretreated with omalizumab for 2 months and then continued throughout the updosing phase. They found that the omalizumab dose per weight alone (median monthly dose, 12.6 mg/kg), in contrast to the dose used to treat asthma per weight and the total IgE level (median monthly dose, 23.1 μg/kg/IgE [IU/mL]), was strongly associated with OIT dose progression through the initial food escalation ($p < 0.0001$).[19] Interestingly, the occurrence of immediate-type reactions to food dosing subsequent

to weaning of omalizumab was significantly associated with a greater ratio of baseline food-specific IgE level to total IgE level.

Thus, there is now mounting evidence that omalizumab facilitates rapid desensitization of OIT updosing phase in both single food and multi-allergen OIT and decreases the rate of allergic reactions. Criteria for selection of patients who would best benefit from such therapy remains to be determined, especially given its significant cost. These patients may include those with a history of severe anaphylaxis, those who desire to rapidly reach maintenance (for travel or other purposes), and possibly those with significant allergic rhinitis because we have noted allergic reactions to OIT during peak allergic rhinitis symptoms in some patients.[17] However, the duration of such therapy still requires further evaluation and may be guided by the adverse events during updosing or the food-specific IgE to total IgE ratio. In addition, omalizumab may have a significant role as monotherapy, particularly in patients with OIT compliance issues; a history of severe allergic reactions to food, chronic urticaria, uncontrolled asthma that renders these patients more susceptible to OIT failure; or in adult patients who are otherwise resistant to OIT. An ongoing phase III, randomized, double-blinded, placebo controlled, multicenter trial is evaluating omalizumab as monotherapy and as adjunct therapy to multi-allergen food OIT (including milk, egg, wheat, cashew, hazelnut, or walnut) (NCT03881696).

Anti–T-Helper Type 2 Cytokine Therapy

Inhibition of T-helper cells type 2 is potential therapeutic target for food allergy. Dupilumab is a monoclonal antibody that binds the interleukin (IL) 4 receptor α chain (IL-4Rα), which, in turn, blocks the signaling of IL-4 and IL-13. A phase II, randomized, placebo controlled clinical trial that is evaluating dupilumab as an adjunct therapy to peanut OIT is ongoing (NCT03682770). Another active trial is comparing the use of omalizumab alone, dupilumab alone, or omalizumab followed by dupilumab therapy in patients on multifood OIT (NCT03679676). Dupilumab also is currently being investigated as monotherapy in a phase II trial in pediatric patients with peanut allergy (NCT03793608).

Bacterial Therapy

Targeting the gut microbiota for treatment of food allergy with mounting evidence of its role in the pathogenesis of food allergy has been of significant interest.[20] We showed, recently, in a highly allergic mouse model, that fecal microbiota transplantation (FMT) or administration of small bacterial consortia of *Bacteroidales* and *Clostridiales* species derived from bacterial strains impacted by the dysbiosis found in infants with food allergy can prevent, treat food allergy, and induces the immunomodulatory RoRγt$^+$Treg cells that are necessary for tolerance.[21] We completed a phase I trial that evaluated the safety and efficacy of FMT in adults with peanut allergy (NCT02960074). Future phase II trials may include evaluation of FMT with and without OIT.

A randomized, double-blind, placebo controlled trial evaluated the use of peanut OIT combined with *Lactobacillus rhamnosus* CGMCC 1.3724 for 18 months.[22] The placebo group received both placebo OIT and placebo probiotics. The primary outcome was to assess sustained unresponsiveness after discontinuation of therapy for a variable period of 2–5 weeks. Sustained unresponsiveness and desensitization were demonstrated in 82% and 89.7%, respectively, of children who received probiotic and peanut OIT compared with 3.6% and 7.1%, respectively, in the placebo group.[22] However, the lack of a comparative treatment arm (peanut OIT with placebo probiotics) was a significant limitation of this study. Subsequently, a recent phase II trial with a more robust design showed no significant difference in sustained unresponsiveness, evaluated 8 weeks after therapy cessation, in the group receiving *L. rhamnosus* CGMCC combined with peanut OIT compared with the group receiving peanut OIT combined with placebo probiotic.[23] A single-center, phase I/II, randomized, double-blind, placebo controlled trial is currently VE416 (a bacterial consortium probiotic) as monotherapy or in combination with peanut OIT in participants ages 12 to 55 years (NCT03936998).

CONCLUSION

Omalizumab is thus far the most investigated biologic as an adjunctive therapy to OIT. There is substantial evidence that omalizumab is effective for rapid desensitization in both single-food and multi-allergen OIT. More limited data are available on biologics, *e.g.*, dupilumab, or bacterial therapy.

CLINICAL PEARLS

- Omalizumab is thus far the most investigated biologic as an adjunctive therapy to OIT.
- There is substantial evidence that omalizumab therapy combined with OIT leads to a more rapid desensitization in both single-food and multi-allergen OIT.
- Other biologics, such as dupilumab and bacterial therapy, are currently being investigated as adjunctive therapies to OIT.

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