



Omalizumab as an adjuvant in food allergen immunotherapy

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Purpose of review

To review the most relevant studies in the rapidly advancing field of omalizumab as an adjunct to food allergen oral immunotherapy (OIT).

Recent findings

Clinical trials have primarily focused on milk, peanut, and multiallergen OIT combined with omalizumab. These studies suggest that omalizumab in addition to OIT can decrease the time required to reach maintenance OIT dosing and adverse events; however, serious adverse events did still occur. There is limited long-term data but available information suggests that individuals are at risk for increased reactivity after stopping omalizumab, and many discontinued treatment. There has been diversity in study designs, dosing, and populations.

Summary

The use of anti-IgE antibody as an adjunct to food allergen OIT has been an expanding area of research with several additional trials underway. Significant progress has been made in the past decades but further studies are needed to optimize protocols, improve safety and efficacy, and identify patients who will have the greatest benefit.

Keywords

anti-IgE, food allergy, immunotherapy, omalizumab, oral immunotherapy

INTRODUCTION

Food allergies have become a significant public health burden affecting 4.8–13% of the United States population [1–3]. Rates of resolution vary depending on a variety of factors but many persist or have low rates of resolution [2]. Current standard-of-care includes avoidance and emergency medications for treatment of reactions. Although highly effective, it can have a significant psychosocial burden [4,5], especially as accidental ingestions can still occur [6]. For these reasons, effective treatment of food allergy would be highly desirable.

Over the past several decades, a significant amount of research has focused on various forms of food immunotherapy [7]. Studies have shown promising results for oral immunotherapy (OIT). OIT protocols vary widely but typically begin with an oral food challenge (OFC), followed by an initial dose escalation (IDE) day, build-up, and then maintenance phase with the goal of slowly inducing desensitization. OIT studies have shown effectiveness for inducing desensitization for milk, egg, peanut, and wheat [7,8,9^a–11^a]; however, there are high rates of episodic allergic reactions that range from

mild, such as oral pruritus, to severe anaphylaxis. Therefore, there is a need to develop safer approaches that will mitigate the risks and/or reduce time to desensitization.

Omalizumab (Xolair) (Novartis, Basel, Switzerland) is a humanized monoclonal anti-IgE antibody that binds to the heavy chain constant C_H3 domain of the free IgE molecule and prevents IgE from binding to FcεRI effector cells [12–14]. This leads to decreased mediator release in response to allergen and the downregulation of FcεRI on mast cells and basophils [13–15]. Omalizumab was initially approved in 2003 for the treatment of severe allergic asthma in adolescents and adults. Labelling has been expanded to asthma down to the age of

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KEY POINTS

- Clinical trials of omalizumab and OIT have primarily focused on milk, peanut, and multiallergen OIT.
- Omalizumab in addition to OIT can decrease the time required to reach maintenance OIT-dosing and adverse events.
- Available information suggests that individuals are at risk for increased reactivity after stopping omalizumab and many discontinued treatment.
- Additional studies are needed to identify the patients who would benefit the most and optimal dosing and duration of therapy.

6 years and for chronic idiopathic urticaria. Omalizumab has been studied as an off-label treatment, or adjunct to treatment, for numerous allergic conditions, including food allergy [16[■],17[■],18–21].

In 2003, Leung *et al.* [22] published the first study to utilize an anti-IgE monoclonal antibody (TNX-901, talizumab) in the treatment of peanut allergy. In this randomized, double-blind, placebo-controlled (DBPC) study, the authors found that talizumab increased the peanut threshold dose from 178 to 2805 mg. Talizumab was not further developed but omalizumab has been studied as both monotherapy [23,24] and as an adjunct to food allergen OIT [25–29,30[■],31,32[■],33–35,36[■]]. Here we will review key studies that have examined the potential benefit of omalizumab in improving efficacy and safety of food allergen OIT (Table 1). Clinical trials have primarily focused on milk, peanut, and multiallergen OIT. Of note, some of these trials have used open-label OIT with the omalizumab component being placebo-controlled. Others have used open-label omalizumab with open-label or placebo-controlled OIT. In addition, the protocols, including OIT dosing and the duration and dosing of omalizumab, have varied across studies.

OMALIZUMAB AND MILK ORAL IMMUNOTHERAPY

The first study of omalizumab combined with milk OIT was performed in 2011 [25]. In this pilot study, 11 children with milk allergy were treated with omalizumab for 9 weeks prior to starting rush oral desensitization (maximum dose of 1000 mg milk powder; cumulative dose of 1992 mg milk powder). Nine of 11 patients (82%) reached 1000 mg on the IDE day and 2000 mg by week 16 and then went on to pass the DBPC food challenge (DBPCFC) to a cumulative dose of 7250 mg of milk, equivalent to

220 ml of milk. In terms of safety, reactions occurred with 1.8% of the doses (41 reactions, 2301 doses), with the most common type of reactions being pruritus, local urticaria, and/or gastrointestinal. Most (70%) were mild, with 20% moderate and 10% severe. This study showed that OIT combined with omalizumab allowed dosing to be escalated more rapidly with a shorter build-up phase than in most OIT studies without omalizumab, but adverse reactions, including the need for epinephrine, still occurred.

The first DBPC trial of omalizumab combined with milk OIT was conducted by Wood *et al.* [26]. Fifty-seven participants, age 7–32 years, were treated with omalizumab or placebo for 4 months and then initiated milk OIT. Open-label milk OIT began with IDE day up to 2.1 mg of milk protein, with dose build-up over 22–40 weeks. Participants then remained on maintenance through month 28 (minimum dose of 520 mg of milk protein, 15 ml). After 12 months of milk OIT (16 months on placebo/omalizumab), treatment was unmasked. Injections stopped for the placebo group. Those in the active group continued omalizumab for an additional 12 months. At month 28, the active group discontinued omalizumab and all participants underwent a DBPCFC to 10 g of milk protein. Participants who passed this challenge, continued milk OIT for an additional 8 weeks. They then stopped milk OIT and 8 weeks later, they underwent a 10 g OFC to evaluate sustained unresponsiveness. There was a significant difference between the omalizumab and placebo groups in doses with symptoms (2.1 vs. 16.1%, $P=0.005$) and dose-related reactions requiring treatment (0 vs. 3.8%, $P=0.0008$). In addition, the omalizumab group required significantly less time (median: 25.9 vs. 30 weeks, $P=0.01$) to achieve maintenance. The study found neither significant differences in the treatment groups in a successful 10 g OFC at month 28 (88.9 vs. 71.4%, $P=0.18$) nor in the 10 g sustained unresponsiveness OFC at month 32 (48.1 vs. 35.7%, $P=0.42$).

Takahashi *et al.* [27] conducted a RCT to evaluate the safety and efficacy of OIT combined with 24 weeks of omalizumab compared with no treatment. All patients in the omalizumab–OIT group tolerated 200 ml of fresh cow's milk during the OFC with a median tolerated dose of 2080 mg during the DBPCFC compared with the untreated group (median: 0 mg). In the OIT build-up phase, 0.012 adverse reactions per dose per child occurred, with no serious adverse events.

Martorell-Calatayud *et al.* [28] treated five patients with milk allergy and nine patients with egg allergy with omalizumab before starting OIT. These children had not previously tolerated

Table 1. Omalizumab combined with oral immunotherapy by food allergen

Author, year [ref. No.]	Study design	Individuals	Omalizumab		Duration	Efficacy outcomes	Safety outcomes
			Initiation				
Milk							
Nadeau <i>et al.</i> , 2011 [25]	Phase 1 pilot study	N = 11 Age: 7–17 years	9 weeks prior to OIT		16 weeks	9/11 individuals reached 2000 mg by week 16 and passed DBPCFC to 3 g (week 24)	Reactions occurred with 1.8% of doses [70% mild, 20% moderate, 10% severe]
Wood <i>et al.</i> , 2016 [26]	DBPC, open-label milk OIT	N = 57 Age: 7–32 years	4 months prior to OIT		28 months	No significant differences in the omalizumab and placebo group in passing a 10 g OFC at month 28 nor in the 10 g SU OFC at month 32 Omalizumab group required less time to reach maintenance	Compared with milk OIT alone, omalizumab group had: - Fewer doses with symptoms - Fewer dose-related reactions requiring treatment - Fewer adverse reactions
Takahashii <i>et al.</i> , 2017 [27]	RCT omalizumab-OIT vs. untreated	N = 16 Age: 6–14y	8 weeks prior to OIT		24 weeks	Omalizumb-OIT group had higher median tolerated dose compared to untreated group during week 32 OFC	- In the OIT build-up phase, 0.012 adverse reactions per dose per child - No serious adverse events.
Martorelli-Calatayud <i>et al.</i> , 2016 [28]	case series	N = 14 (5 milk allergy; 9 egg allergy) Age: 3–13 years	9 weeks prior to OIT		Stopped 2 months after reaching the final dose of the induction phase	All achieved complete desensitization at the end of the induction phase (200 ml milk = 6.6 g milk protein; or 17 ml liquid raw egg white = 1.8g egg protein) 3/5 (60%) on milk OIT and 3/9 (33%) on egg OIT had a decrease in tolerated dose after stopping omalizumab	- In the OIT induction phase, 4/14 had mild reactions. - 6 patients had anaphylactic symptoms 2.4 to 4 months after stopping omalizumab
Peanut							
Schneider <i>et al.</i> , 2013 [29] Yee <i>et al.</i> , 2019 [30■]	Pilot Study, open-label Long-term follow-up study	N = 13 Age: 8–16 years	12 weeks prior to OIT		20 weeks	All reached 500 mg dose on IDE - 12/13 individuals reached max maintenance dose of 4000 mg and passed OFC to 8000 mg (12 weeks after stopping omalizumab, on OIT) - ITFU: 7/12 (58%) continued peanut OIT at month 72	Reactions occurred with 2% of doses [87.5% mild] 49 reactions during up-dosing on omalizumab: 96% mild, 4% moderate. 17 reactions during maintenance off omalizumab: 10 mild, 5 moderate, 2 severe. - ITFU: all patients had at least one adverse reaction [86% mild, 12 (5%) treated with epinephrine] One patient diagnosed with EoE
Brandström <i>et al.</i> , 2019 [32■]	One-armed phase 2 trial	N = 23 Age: 12–19 years	8–24 weeks prior to OIT depending on CD-sens		At least 8 weeks (variable based on symptoms and CD-sens)	All reached 2800 mg maintenance dose 9/23 (39%) tolerated a 2800 mg single-dose challenge 12 weeks after stopping omalizumab	Mild oropharyngeal and GI symptoms were common Systemic reactions occurred with 0.3% of doses (n = 43), with 4/43 occurring while patient was on full-dose omalizumab One patient diagnosed with EoE

Table 1 (Continued)

Author, year [ref. No.]	Study design	Individuals	Omalizumab		Efficacy outcomes	Safety outcomes
			Initiation	Duration		
MacGinnitie <i>et al.</i> , 2017 [33]	DBPC, open-label peanut OIT	N = 37 Age: 7–19 years	12 weeks prior to OIT	19–25 weeks	Increased efficacy in the omalizumab group: Higher median peanut dose tolerated on IDE Higher percentage tolerated 2000 mg 6 weeks after stopping study drug (79 vs. 12.5%) -Higher percentage tolerated 4000 mg 12 weeks after stopping study drug (76 vs. 12.5%)	No significant difference between groups in frequency of dosing reactions. Three individuals (two on omalizumab, one placebo) stopped OIT because of concern for EoE (2/3 biopsy proven)
Multifood						
Bégin <i>et al.</i> , 2014 [34]	Phase 1 open-label	N = 25 Age: 4–15 years	8 weeks prior to OIT	16 weeks	76% reached maximum dose of 1250 mg on IDE Median time to maintenance dose: 18 weeks All participants reached a 10-fold increase in dose of all their allergens by 2 months of therapy	94% of all reactions were mild -52% had some symptoms during IDE -Reaction with 5.3% of home doses
Andorf <i>et al.</i> , 2018 [35]	DBPC phase 2 and open-label OIT	N = 48 Age: 4–15 years	8 weeks prior to OIT	16 weeks	Compared with placebo, omalizumab group: Greater median tolerated dose on IDE Reached maintenance faster Greater proportion passed DBPCFC to 2000 mg protein for at least two and four foods (week 36)	Fewer dosing-related adverse events while receiving omalizumab compared with OIT with placebo No increase in adverse events after stopping omalizumab No serious or severe adverse events in either group

DBPCFC, double-blind, placebo-controlled food challenge; EoE, eosinophilic esophagitis; IDE, initial dose escalation; ITFU, long-term follow-up; OFC, oral food challenge; OIT, oral immunotherapy; RCT, randomized control trial; SU, sustained unresponsiveness.

conventional milk or egg OIT because of anaphylactic reactions. Patients were treated with omalizumab before re-starting OIT. All patients achieved complete desensitization. However, 3/5 (60%) on milk OIT and 3/9 (33%) on egg OIT had a decrease in the threshold dose eliciting allergic reactions after stopping omalizumab.

OMALIZUMAB AND PEANUT ORAL IMMUNOTHERAPY

Schneider *et al.* [29] performed a pilot study of omalizumab as an adjuvant to peanut OIT. Thirteen peanut allergic children (age 8–16 years) received omalizumab for 12 weeks, followed by a 1-day rush IDE of up to a 500 mg of peanut flour (cumulative dose of 992 mg). Over weeks 12–20, participants increased their dose up to 4000 mg. At week 20, all stopped omalizumab and continued peanut OIT. Twelve weeks later, individuals had a DBPCFC to 8000 mg of peanut flour. All 13 individuals reached the 500 mg dose on the IDE day. Twelve of 13 individuals reached the maximum maintenance dose of 4000 mg of peanut flour (median time of 8 weeks). All 12 then tolerated a cumulative dose of 8000 mg (about 20 peanuts) 12 weeks after stopping omalizumab and then started to consume 10–20 peanuts per day. One subject dropped out at week 15 because of persistent nausea and vomiting. Reactions occurred with 2% of doses ($n=72$; mean of 5.5 reactions per child), but the majority were mild (87.5%) and occurred during weekly dose escalation (65%). Seven of 13 children had no reaction during the rush IDE. During maintenance, there were 17 reactions after discontinuing omalizumab (10 mild, 5 moderate, 2 severe). No severe reactions occurred while receiving omalizumab. During months 12–72, 12 individuals participated in the long-term follow-up (LTFU) study [30^{***}]. Individuals were not on omalizumab and could consume commercial peanut products. The authors concluded that although omalizumab allowed for faster and effective desensitization, only 7 of 13 initially enrolled (54%) were consuming peanut at month 72.

Brandström *et al.* [31,32^{***}] published a one-armed phase 2 trial of peanut OIT facilitated by individually dosed omalizumab. In the first part of the study, 23 peanut-allergic adolescents (age 12–19 years), were treated with omalizumab for 8–24 weeks depending on basophil allergen threshold sensitivity (CD-sens) and symptoms [31]. In the second part of the trial, participants ($n=23$) were started on peanut OIT while remaining on individually dosed omalizumab [32^{***}]. Peanut OIT started at 280 mg of peanut protein and increased every

2 weeks until the goal dose of 2800 mg. After stopping omalizumab, individuals continued on peanut OIT for 12 weeks and then had an in-hospital single-dose peanut challenge with their current OIT dose. If a subject could not stop omalizumab after 4 years from study start, then they were considered a treatment failure. All reached the 2800 mg maintenance dose in a median of 10 weeks. Nine of 23 individuals (39%) were able to tolerate 2800 mg of peanut protein for 12 weeks after stopping omalizumab and had a negative single dose challenge to 2800 mg. Two completed the study with decreased doses of peanut because of taste aversion. Six individuals dropped out. Six individuals were unable to stop omalizumab. Mild oropharyngeal and abdominal symptoms were common. Systemic reactions occurred with 0.3% of doses ($n=43$), with 39/43 (91%) occurring after patient was no longer on full-dose omalizumab and the single severe systemic reaction occurring after omalizumab had been discontinued. One patient accounted for 33% of the systemic reactions. In addition, one patient developed swallowing difficulties and was found to have biopsy-proven eosinophilic esophagitis (EoE) that improved after stopping peanut OIT.

The first randomized, DBPC, multicenter study of the efficacy of omalizumab combined with peanut OIT was performed by MacGinnitie *et al.* [33]. Thirty-seven individuals (age 7–19 years) were randomized to omalizumab ($n=29$) or placebo ($n=8$) combined with peanut OIT. Patients received study drug for 12 weeks and then had a rapid oral IDE day up to 250 mg of peanut protein (cumulative 490.5 mg). Individuals increased the dose one to two times per week up to 2000 mg. Those on omalizumab tolerated more than 10 times higher median protein dose during the IDE compared with the placebo group (250 vs. 22.5 mg, $P<0.01$). In the intention-to-treat (ITT) analysis, 23/29 (79%) individuals randomized to omalizumab and 1/8 (12.5%) receiving placebo achieved the primary endpoint (tolerating 2000 mg of peanut protein 6 weeks after stopping omalizumab or placebo) ($P<0.01$). Similarly, 22/29 (76%) in the omalizumab group and 1/8 (12.5%) in the placebo group passed the OFC to 4000 mg of peanut protein 12 weeks after stopping the study drug ($P<0.01$). There was no significant difference between the groups in frequency of dosing reactions despite the higher peanut doses consumed in the omalizumab group (odds ratio: 0.57, $P=0.15$). Most reactions were mild and occurred during the IDE day and build-up. However, moderate and severe reactions did still occur in both groups, including 11 reactions that required epinephrine in patients on omalizumab. Three individuals (two on omalizumab, one on placebo) stopped

peanut OIT because of persistent gastrointestinal symptoms concerning for EoE. Two of three patients had an esophageal biopsy and both had results consistent with EoE.

OMALIZUMAB AND MULTIFOOD ORAL IMMUNOTHERAPY

Among food-allergic children and adults, surveys suggest that up to 45% are allergic to multiple foods [3,37]. For that reason, there is interest in treating multiple allergies simultaneously [38]. Bégin *et al.* [34] conducted the first study of multifoed OIT combined with omalizumab. Twenty-five peanut allergic patients (age 4–15 years) participated in this open-label phase 1 study of rush OIT after pretreatment with omalizumab. Individuals received omalizumab for 8 weeks prior to and 8 weeks after starting OIT. Individuals completed rapid oral desensitization to up to five food allergens (250 mg of each food protein; up to 1250 mg of total food protein) and then returned every 2 weeks for dose increases up to 4000 mg per allergen. Although 13/25 (52%) had some symptoms during the IDE, 19/25 (76%) were able to reach the maximum dose of 1250 mg of total food protein. The median time to reach the maintenance dose was 18 weeks (7–36). There was a median reaction rate of 3.2 per 100 doses taken at home, with most occurring in the first months of therapy. About 94% of allergic reactions were mild. One patient had a severe reaction that occurred shortly after reaching maintenance.

Andorf *et al.* [35] conducted a blinded, phase 2 trial of multifoed OIT combined with omalizumab ($n=36$) or placebo ($n=12$). They enrolled 48 patients (age 4–15 years) who received omalizumab or placebo for 16 weeks. At week 8, they started OIT for two to five foods. Individuals underwent DBPCFC at week 36. Treatment failures ($n=11$) started open-label omalizumab at week 17. Those on omalizumab had a greater median-tolerated dose on the IDE day (250 vs. 11.25 mg per food, $P<0.0001$) and reached maintenance faster compared with those on placebo ($P=0.001$). In addition, a greater proportion of the omalizumab vs. placebo individuals passed the week 36 DBPCFCs to 2 g protein for ≥ 2 foods (83 vs. 33%, $P=0.004$) and for at least four foods (77 vs. 0%, $P=0.01$). All individuals who tolerated 2 g for at least two foods also tolerated 4 g for at least two foods in the same challenges ($P=0.004$). During weeks 8–16 (on omalizumab/placebo and OIT), those on omalizumab had a lower median per-participant percentage of OIT doses associated with adverse events compared with placebo (27 vs. 68%) and specifically had fewer doses associated with gastrointestinal (22 vs. 54%,

$P=0.04$) or respiratory symptoms (0 vs. 1%, $P=0.02$). Adverse events did not increase during the period of omalizumab withdrawal. There were no serious or severe adverse events in either group. The authors concluded that multifoed OIT combined with an initial course of omalizumab assisted in effective rapid desensitization to multiple foods.

A multicenter phase 2 study evaluated three OIT maintenance doses (0, 300, and 1000 mg) after omalizumab combined with multiallergen OIT [36[†]]. This study enrolled 70 participants, aged 5–22 years, with multiple food allergies. The open-label phase of the study included omalizumab (weeks 0–16) and OIT (weeks 8–30). Individuals underwent OFCs at week 30 and were then randomized to maintenance OIT dosing with 1000, 300, or 0 mg per allergen. Food challenges were repeated at week 36. The authors conclude that further studies are needed to determine the optimal maintenance dose needed to maintenance tolerance after omalizumab-facilitated multiallergen OIT.

UNITED STATES TRIALS IN PROGRESS

In addition, several studies are currently active in the United States. NCT02879006 is a phase 2 DBPC multisite study that aims to evaluate the use of Chinese herbal formula, E-B-FAHF-2, in combination with omalizumab and multifoed OIT. All individuals will receive multiallergen OIT combined with omalizumab for the initial 4 months and then be randomized to receive active Chinese herbal formula or placebo. Individuals will be treated with OIT for 2 years and then undergo OFC. Those who achieve desensitization, will stop all treatments and then repeat food challenges 3 months later to determine if they have sustained unresponsiveness. The primary endpoint is defined as developing sustained unresponsiveness to all three study food allergens, defined as no dose-limiting symptoms to a cumulative dose of 4444 mg protein after stopping all treatments for 3 months. The estimated study completion date is November 2020.

NCT03881696, ‘Omalizumab as Monotherapy and as Adjunct Therapy to Multi-Allergen OIT in Food Allergic Children and Adults- OUTMATCH’, is a phase 3 DBPC multisite study that aims to determine the safety and efficacy of omalizumab alone or in combination with multiallergen OIT (peanut combined with two additional foods) in the treatment of food allergy. The study involves the completion of baseline OFCs and then three stages. In stage 1, individuals will be randomized to omalizumab or placebo for 16 weeks. They will then repeat the DBPCFCs. The initial 60 patients will then receive 24–28 weeks of open-label omalizumab

Table 2. Advantages and limitations of addition of omalizumab to oral immunotherapy

Advantages	Limitations/needs for further research
Decreased time required to reach maintenance dose	Cost
Fewer reactions while receiving OIT combined with omalizumab compared with OIT without omalizumab	Many unknowns related to omalizumab: Best dose Best timing prior to initiation of OIT Best duration Lack of long-term data – to date, does not appear to impact long-term safety, efficacy, or sustained unresponsiveness Dosing limitations because of elevated total IgE and weight

OIT, oral immunotherapy.

and then repeat DBPCFCs. In stage 2, all individuals will receive 8 weeks of open-label omalizumab. After 8 weeks, individuals will be randomized 1:1 to 1) omalizumab-facilitated OIT or omalizumab combined with placebo OIT. Individuals will repeat DBPCFCs at week 52. In stage 3, individuals will receive an individualized treatment plan for dietary consumption. The estimated completion date is December 2023.

CONCLUSION

The use of anti-IgE antibody as an adjunct to food allergen OIT has been an expanding area of research over the past two decades (Table 2). To date, studies are limited, and there has been tremendous variability in the study design and drug administration – open-label vs. placebo-controlled, initiation and duration of treatment, overlap of omalizumab and OIT, timing of OFCs after stopping omalizumab. These studies suggest that omalizumab in addition to OIT can decrease the time required to reach maintenance OIT-dosing and adverse events; however, serious adverse events did still occur. There is limited long-term data but available information suggests that individuals are at risk for increased reactivity after stopping omalizumab and many discontinued treatment. It is an exciting time in the field of food allergy research as the use of biologics and food allergen immunotherapy are interwoven to try to improve safety and maximize efficacy but many unanswered questions remain. Future studies should aim to identify the patients who would benefit the most from the addition of omalizumab to OIT. In addition, the optimal dosing and duration of therapy is unknown, which is highly significant, given the cost of this medication [39**]. Perhaps most importantly, more data is needed to determine if omalizumab changes long-term outcomes.

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Conflicts of interest

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REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

- Dunlop JH, Keet CA. Epidemiology of food allergy. *Immunol Allergy Clin North Am* 2018; 38:13–25.
 - Sicherer SH, Sampson HA. Food allergy: a review and update on epidemiology, pathogenesis, diagnosis, prevention, and management. *J Allergy Clin Immunol* 2018; 141:41–58.
 - Gupta RS, Warren CM, Smith BM, *et al.* Prevalence and severity of food allergies among US adults. *JAMA Netw Open* 2019; 2:e185630.
 - Dantzer JA, Keet CA. Anxiety associated with food allergy in adults and adolescents: an analysis of data from the National Health and Nutrition Examination Survey (NHANES) 2007-2010. *J Allergy Clin Immunol Pract* 2020; 8:1743.e5–1746.e5.
 - Primeau MN, Kagan R, Joseph L, *et al.* The psychological burden of peanut allergy as perceived by adults with peanut allergy and the parents of peanut-allergic children. *Clin Exp Allergy* 2000; 30:1135–1143.
 - Blom WM, Michelsen-Huisman AD, van Os-Medendorp H, *et al.* Accidental food allergy reactions: products and undeclared ingredients. *J Allergy Clin Immunol* 2018; 142:865–875.
 - Burks AW, Sampson HA, Plaut M, *et al.* Treatment for food allergy. *J Allergy Clin Immunol* 2018; 141:1–9.
 - Wood RA. Food allergen immunotherapy: current status and prospects for the future. *J Allergy Clin Immunol* 2016; 137:973–982.
 - Soller L, Abrams EM, Carr S, *et al.* First real-world safety analysis of preschool peanut oral immunotherapy. *J Allergy Clin Immunol Pract* 2019; 7:2759.e5–2767.e5.
- This study found that peanut OIT in preschool children appeared well tolerated for most.
- Makita E, Yanagida N, Sato S, *et al.* Long-term prognosis after wheat oral immunotherapy. *J Allergy Clin Immunol Pract* 2020; 8:371.e5–374.e5.
- This study reported the long-term outcomes for patients who received wheat OIT and found that exercise-related allergic reactions were not rare and 42% of patients had an adverse allergic reaction during the 2-year follow-up.

11. Nowak-Węgrzyn A, Sato S, Fiocchi A, Ebisawa M. Oral and sublingual immunotherapy for food allergy. *Curr Opin Allergy Clin Immunol* 2019; 19:606–613.

This article reviews key studies in food allergen-specific immunotherapy.

12. Kawakami T, Blank U. From IgE to Omalizumab. *J Immunol* 2016; 197:4187–4192.
13. MacGlashan D. Loss of receptors and IgE in vivo during treatment with anti-IgE antibody. *J Allergy Clin Immunol* 2004; 114:1472–1474.
14. Saini SS, MacGlashan DW, Sterbinsky SA, et al. Down-regulation of human basophil IgE and FC epsilon RI alpha surface densities and mediator release by anti-IgE-infusions is reversible in vitro and in vivo. *J Immunol* 1999; 162:5624–5630.
15. MacGlashan DW, Bochner BS, Adelman DC, et al. Down-regulation of Fc(epsilon)RI expression on human basophils during in vivo treatment of atopic patients with anti-IgE antibody. *J Immunol* 1997; 158:1438–1445.
16. Humbert M, Bousquet J, Bachert C, et al. IgE-mediated multimorbidities in allergic asthma and the potential for omalizumab therapy. *J Allergy Clin Immunol Pract* 2019; 7:1418–1429.

This article reviews the recent evidence for the use of omalizumab in the treatment of multiple allergic conditions, including food allergies.

17. Dantzer JA, Wood RA. Next-generation approaches for the treatment of food allergy. *Curr Allergy Asthma Rep* 2019; 19:5.

This article reviews new approaches to the treatment of food allergy, including the use of immunomodulatory agents.

18. El-Qutob D. Off-label uses of omalizumab. *Clin Rev Allergy Immunol* 2016; 50:84–96.
19. Dantzer JA, Wood RA. The use of omalizumab in allergen immunotherapy. *Clin Exp Allergy* 2018; 48:232–240.
20. Long A, Borro M, Sampath V, Chinthrajah RS. New developments in non-allergen-specific therapy for the treatment of food allergy. *Curr Allergy Asthma Rep* 2020; 20:3.
21. Sampath V, Sindher SB, Alvarez Pinzon AM, Nadeau KC. Can food allergy be cured? What are the future prospects? *Allergy* 2020; 75:1316–1326.
22. Leung DY, Sampson HA, Yunginger JW, et al. Effect of anti-IgE therapy in patients with peanut allergy. *N Engl J Med* 2003; 348:986–993.
23. Savage JH, Courneya JP, Sterba PM, et al. Kinetics of mast cell, basophil, and oral food challenge responses in omalizumab-treated adults with peanut allergy. *J Allergy Clin Immunol* 2012; 130:1123.e2–1129.e2.
24. Sampson HA, Leung DY, Burks AW, et al. A phase II, randomized, double-blind, parallel-group, placebo-controlled oral food challenge trial of Xolair (omalizumab) in peanut allergy. *J Allergy Clin Immunol* 2011; 127:1309.e1–1310.e1.
25. Nadeau KC, Schneider LC, Hoyte L, et al. Rapid oral desensitization in combination with omalizumab therapy in patients with cow's milk allergy. *J Allergy Clin Immunol* 2011; 127:1622–1624.
26. Wood RA, Kim JS, Lindblad R, 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; 137:1103.e11–10.e11.

27. 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.

28. Martorell-Calatayud C, Michavila-Gómez A, Martorell-Aragonés A, et al. Anti-IgE-assisted desensitization to egg and cow's milk in patients refractory to conventional oral immunotherapy. *Pediatr Allergy Immunol* 2016; 27:544–546.

29. Schneider LC, Rachid R, LeBovidge J, et al. A pilot study of omalizumab to facilitate rapid oral desensitization in high-risk peanut-allergic patients. *J Allergy Clin Immunol* 2013; 132:1368–1374.

30. Yee CSK, Albuhairei S, Noh E, et al. Long-term outcome of peanut oral immunotherapy facilitated initially by omalizumab. *J Allergy Clin Immunol Pract* 2019; 7:451.e7–461.e7.

This is one of the few studies to evaluate long-term outcomes in those treated with omalizumab and oral immunotherapy.

31. Brandström J, Vetander M, Lilja G, et al. Individually dosed omalizumab: an effective treatment for severe peanut allergy. *Clin Exp Allergy* 2017; 47:540–550.

32. Brandström J, Vetander M, Sundqvist AC, et al. Individually dosed omalizumab facilitates peanut oral immunotherapy in peanut allergic adolescents. *Clin Exp Allergy* 2019; 49:1328–1341.

This article describes a phase-2 study of individualized omalizumab treatment and peanut OIT. This study describes a unique approach to omalizumab dosing based on CD-sens.

33. MacGinnitie AJ, Rachid R, Gragg H, et al. Omalizumab facilitates rapid oral desensitization for peanut allergy. *J Allergy Clin Immunol* 2017; 139:873.e8–881.e8.

34. Bégin P, Dominguez T, Wilson SP, et al. Phase 1 results of safety and tolerability in a rush oral immunotherapy protocol to multiple foods using Omalizumab. *Allergy Asthma Clin Immunol* 2014; 10:7.

35. Andorf S, Purington N, Block WM, et al. Anti-IgE treatment with oral immunotherapy in multifood allergic participants: a double-blind, randomised, controlled trial. *Lancet Gastroenterol Hepatol* 2018; 3:85–94.

36. Andorf S, Purington N, Kumar D, et al. A phase 2 randomized controlled multisite study using omalizumab-facilitated rapid desensitization to test continued vs discontinued dosing in multifood allergic individuals. *EClinical-Medicine* 2019; 7:27–38.

This study aims to determine the optimal maintenance dose needed to maintain tolerance after omalizumab-facilitated multiallergen OIT and determined that some tolerance was maintained after stopping omalizumab in all groups.

37. Gupta RS, Springston EE, Warrier MR, et al. The prevalence, severity, and distribution of childhood food allergy in the United States. *Pediatrics* 2011; 128:e9–e17.

38. Wood RA. Oral immunotherapy for food allergy. *J Invest Allergol Clin Immunol* 2017; 27:151–159.

39. Azzano P, Paquin M, Langlois A, et al. Determinates of omalizumab dose-related efficacy in oral immunotherapy: evidence from a cohort of 181 patients. *J Allergy Clin Immunol* 2021; 147:233–243.

This study uses a large cohort to provide data on the optimal omalizumab-dosing strategy and prognostic factors. The authors recommend that omalizumab dosing should be based on weight alone.