Anti-IgE treatment with oral immunotherapy in multifood allergic participants: a double-blind, randomised, controlled trial

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Summary

Background Despite progress in single food oral immunotherapy, there is little evidence concerning the safety and efficacy of treating individuals with multiple food (multifood) allergies. We did a pilot study testing whether anti-IgE (omalizumab) combined with multifood oral immunotherapy benefited multifood allergic patients.

Methods We did a blinded, phase 2 clinical trial at Stanford University. We enrolled participants, aged 4–15 years, with multifood allergies validated by double-blind, placebo-controlled food challenges to their offending foods. Inclusion criteria included a positive skin prick test of 6 mm or more (wheal diameter, above the negative control), a food-specific serum IgE concentration of more than 4 kU/L for each food, or both, and a positive double-blind, placebo-controlled food challenge at 500 mg or less of food protein. Exclusion criteria included eosinophilic oesophagitis and severe asthma. Participants were randomised (3:1) with a block size of four, to receive multifood oral immunotherapy to two to five foods, together with omalizumab (n=36) or placebo (n=12). 12 individuals who fulfilled the same inclusion and exclusion criteria were included as controls. These individuals were not randomised and received neither omalizumab nor oral immunotherapy. Omalizumab or placebo was administered subcutaneously for 16 weeks, with oral immunotherapy starting at week 8, and was stopped 20 weeks before the exit double-blind, placebo-controlled food challenge at week 36. The primary endpoint was the proportion of participants who passed double-blind, placebo-controlled food challenges to at least two of their offending foods. This completed trial is registered with ClinicalTrials.gov, number NCT02643862.

Findings Between March 25, 2015, and Aug 18, 2016, 165 participants were assessed for eligibility, of whom 84 did not meet the inclusion criteria and 21 declined to participate. We enrolled and randomised 48 eligible participants and the remaining 12 patients were included as nonrandomised, untreated controls. At week 36, a significantly greater proportion of the omalizumab-treated (30 [83%] of 36) versus placebo (four [33%] of 12) participants passed double-blind, placebo-controlled food challenges to 2 g protein for two or more of their offending foods (odds ratio 10·0, 95% CI 1·8–58·3, p=0·0044). All participants completed the study. There were no serious or severe (grade 3 or worse) adverse events. Participants in the omalizumab group had a significantly lower median per-participant percentage of oral immunotherapy doses associated with any adverse events (27% *vs* 68%; p=0·0082). The most common adverse events in both groups were gastrointestinal events.

Interpretation In multifood allergic patients, omalizumab improves the efficacy of multifood oral immunotherapy and enables safe and rapid desensitisation.

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Introduction

Approximately 30% of food allergic individuals have multiple food allergies (multifood allergies).[1] The development of more efficacious food allergy treatments is particularly important for such patients because the co-occurrence of multifood allergies increases risks for accidental ingestions and near-fatal or fatal anaphylaxis.[1] Although many studies have evaluated the efficacy of oral immunotherapy for single foods, studies evaluating oral immunotherapy for multiple foods have been limited due to efficacy and safety concerns.[2–6]

Omalizumab (Xolair, Genetech, San Francisco, CA, USA), a recombinant DNA-derived humanised IgG_1 monoclonal antibody that selectively binds human IgE, inhibits binding of IgE to high-affinity IgE receptors (FceRIs) on the surface of mast cells and basophils, downregulates expression of the receptor, and reduces blood levels of free IgE.[7,8] Studies[9–12] have shown that food allergy desensitisation can be achieved relatively rapidly when single oral immunotherapy is combined with omalizumab in individuals who are allergic to single foods. A phase 1 safety study[13] reported that initial dosing with omalizumab (for the first 16 weeks of a 40 week oral immunotherapy regimen) increased the initial dose of food protein that could be used during rapid milk oral immunotherapy. A subsequent study[9] showed that combining omalizumab with milk oral

Research in context

Evidence before this study

We searched PubMed with the terms "multiple food allergy", "food allergy and omalizumab", and "oral immunotherapy" for articles published on or before Oct 1, 2017, with no start date or language restrictions. We found two pilot clinical trials using omalizumab with single allergen oral immunotherapy to either milk or peanut. The only multiple allergen oral immunotherapy protocol using omalizumab was our original phase 1 publication about the safety and tolerability of an oral immunotherapy protocol to multiple foods using omalizumab. However, that study did not include a placebo arm.

Added value of this study

To our knowledge, this is the first phase 2, randomised, controlled study to investigate the efficacy and safety of omalizumab combined with multifood allergen oral immunotherapy. Our approach addresses a crucial need for effective concomitant multifood desensitisation in a highly atopic population with multiple allergies, who are at risk for near-fatal or fatal food allergic reactions.

Implications of all the available evidence

Our findings provide evidence that patients with multifood allergies can be safely and effectively desensitised to their offending foods with a combination of multifood oral immunotherapy with omalizumab treatment. These results will potentially affect clinical practice and inform future trials using omalizumab as an adjunct medication with food allergen immunotherapy for patients with food allergies.

immunotherapy significantly improved safety outcomes in the omalizumab versus placebo group. Significant improvements in the efficacy of oral immunotherapy with initial omalizumab (versus placebo) treatment were also reported in a phase 2 clinical trial[10] implementing rapid peanut oral immunotherapy.

Because multifood allergic individuals could benefit from treatment and omalizumab potentially mitigates their risk for IgE-mediated allergic reactions, we designed a randomised, placebo-controlled phase 2 study to determine whether initial use of omalizumab (beginning 8 weeks before starting multifood oral immunotherapy) improves the efficacy of multifood oral immunotherapy compared with immunotherapy alone, as determined by a double-blind, placebo-controlled food challenge ("food challenge" hereafter) at 36 weeks.

See Online for appendix

Methods

Study design

We did a randomised, double-blind, placebo-controlled, phase 2 clinical trial at the Sean N Parker Center for Allergy and Asthma Research at Stanford University from March 25, 2015, to Aug 18, 2016, with Stanford IRB approval under IND 14831. Eligible participants were randomised 3:1 to receive omalizumab (dosed per product insert) or placebo for 16 weeks, after which treatment was discontinued. Multifood oral immunotherapy consisting of equal parts of up to five offending foods was administered from weeks 8 through 36, with updosing to a maintenance dose of 2 g per food. Cashew, walnut, hazelnut, almond, sesame, cow's milk, hen's egg, peanut, soy, and wheat were included as foods in this study. The term multifood can refer to distinct foods or, for example, several different tree nuts. A control group of 12 individuals who fulfilled the same inclusion and exclusion criteria were included as a comparison group for the studies evaluating change of IgE and IgG_4 levels and the IgG_4/IgE ratio as well as skin prick test wheal diameter changes from baseline to post oral immunotherapy in the study successes. The study was monitored by an independent Data and Safety Monitoring Board (DSMB) provided by the US National Institutes of Health (NIH; DAIT DSMB) and an independent NIH Medical Monitor.

Participants

We enrolled participants aged 4–15 years who had food challenge-proven allergies to more than one food. Inclusion criteria included a positive skin prick test of 6 mm or more (wheal diameter, above the negative control), a food-specific serum IgE concentration of more than 4 kU/L for each food, or both, and a positive (failed) food challenge at 500 mg or less of food protein. Exclusion criteria included eosinophilic oesophagitis and severe asthma. A full list of inclusion and exclusion criteria is shown in the appendix (pp 42–44). Participants were recruited from referrals into a single study site (ie, Stanford) and from a waitlist of eligible individuals that was selected randomly for screening. Written informed consent was obtained before randomisation.

Randomisation and masking

Eligible participants were randomly assigned 3:1 to omalizumab or placebo, using a computer and 4×4 block randomisation. Randomisation to receive omalizumab or placebo was stratified by sex and prepared by a blinded biostatistician. 3:1 randomisation between omalizumab and placebo was chosen to improve expected compliance, while also providing large enough sample sizes for the statistical analysis. Unblinding of randomisation assignments or during food challenges was specified to take place only in the event of a complication or if the principal investigator or DSMB determined that unblinding was necessary. During the course of the study, no unblinding was needed. Upon completion of each participant's end-of-study visit and confirmation of data entry lock, study staff submitted a formal request for participant-specific

unblinding. This formal request was sent to the Stanford Investigational Pharmacist at the time of unblinding.

Procedures

All participants were screened using published, standardised procedures of skin prick tests, specific IgE tests, and food challenges, as detailed in the protocol. Food challenges were done using standardised, validated, staged doses and were deemed positive if objective symptoms were diagnosed by trained personnel. Participants underwent baseline food challenges (and week 36 food challenges) for single offending foods on separate days. The foods included in each participant's multifood oral immunotherapy included those for which the participant had a significant allergic reaction to a 500 mg or less cumulative dose of food protein in the individual food challenges done at baseline. Participants could have up to five foods included in their multifood oral immunotherapy regimen. For those participants with allergies to more than five foods, the foods chosen for the multifood oral immunotherapy regimen were those which, on screening, were associated with a lower cumulative tolerated dose in the baseline food challenges, and those for which the participant had a relatively higher specific IgE concentration, or a larger skin prick test wheal diameter (or both) compared with other food allergens. Additionally, for those participants who had both cashew and pistachio or walnut and pecan food allergy, only cashew or walnut was included in the multifood oral immunotherapy. This way, at the end of the study, we could test for the possible ability of cashew oral immunotherapy to desensitise to both cashew and pistachio or of walnut oral immunotherapy to desensitise to both walnut and pecan in relevant individuals. Adverse events and drug relatedness were evaluated by a trained physician. Dosing of omalizumab was given according to the manufacturer's instructions and the product insert. The initial dose escalation day was defined as the first day of dosing with oral immunotherapy; patients could receive multiple doses of each food on this day. On the initial dose-escalation day patients received an initial dose of 5 mg food protein (divided equally among the number of foods included), with increasing doses administered every 30 min until reaching 1250 mg or a maximum-tolerated dose. The participants then continued at-home self-administration of the combined oral immunotherapy at the maximum-tolerated dose, returning every 2–4 weeks for an increase in their daily dose (build-up phase). When participants reached the maintenance dose of 2 g per food, this dose was maintained daily (maintenance phase) until the food challenge at week 36 (full details of the oral immunotherapy procedure are in the appendix pp 56–63). Follow-up intervals were approximately every 2–4 weeks and assessments included skin prick tests, blood tests, physical examinations, diary reviews, adverse events, dose escalations, food challenges, and spirometry.

Outcomes

The primary endpoint was the proportion of participants who passed a food challenge at 36 weeks (ie, no clinical reactivity to 2 g of protein) for any two foods included in each participant's oral immunotherapy regimen. Study failure was defined as not reaching the primary endpoint. The failures were further divided into treatment or desensitisation failures. Treatment failure was defined by failure to tolerate 5 mg of food protein (total) during the initial dose escalation day (week 8); failure to reach at least 300 mg of total protein by week 16; or as determined by the principal investigator or medical monitor. Desensitisation failure was defined by inability to ingest 2 g or more of each offending food at week 34, and therefore unable to undergo the week 36 food challenges; severe reactions at least 4 weeks before week 36; or clinical reactivity (grade 1 or worse) during the food challenge to 2 g of all, or all but one, of the foods included in the participant's multifood oral immunotherapy regimen at week 36. All study failures were followed until the final specified study visit and monitored for adverse events but no longer underwent food challenges. Treatment failures were offered open-label omalizumab, starting in week 17 (appendix p 5).

Secondary endpoints were the proportion of participants who passed a food challenge to 4 g each of at least two foods at week 36; the proportion of participants who passed a food challenge to 2 g each of three, four, or five foods at week 36; the proportion of participants who successfully completed the build-up phase of oral immunotherapy to the highest dose (2 g of each protein) with only mild (grade 1) symptoms; and the proportion of participants who successfully underwent the build-up and maintenance phases of oral immunotherapy with only mild symptoms. The remaining secondary endpoints listed in the protocol could not be analysed because most participants did not agree to further food challenge escalation past 4 g of each food due to the length of time that would have been needed (more than 8 h total).

Safety outcomes were determined by Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 criteria and documented per regulatory guidelines. We measured skin prick test wheal sizes and allergen-specific IgE and IgG_4 levels, and assessed relationships to safety and efficacy outcomes and changes over time. Cross-desensitisation (operationally defined herein as desensitisation against a related allergenic food to which the participant is allergic but which was not included in the multifood oral immunotherapy) was also evaluated.

Statistical analysis

Sample size considerations can be found in the appendix (p 2). All analyses were done according to the intention-to-treat (ITT) principle. A central two-sided Fisher's exact test was used to compare the proportion of participants

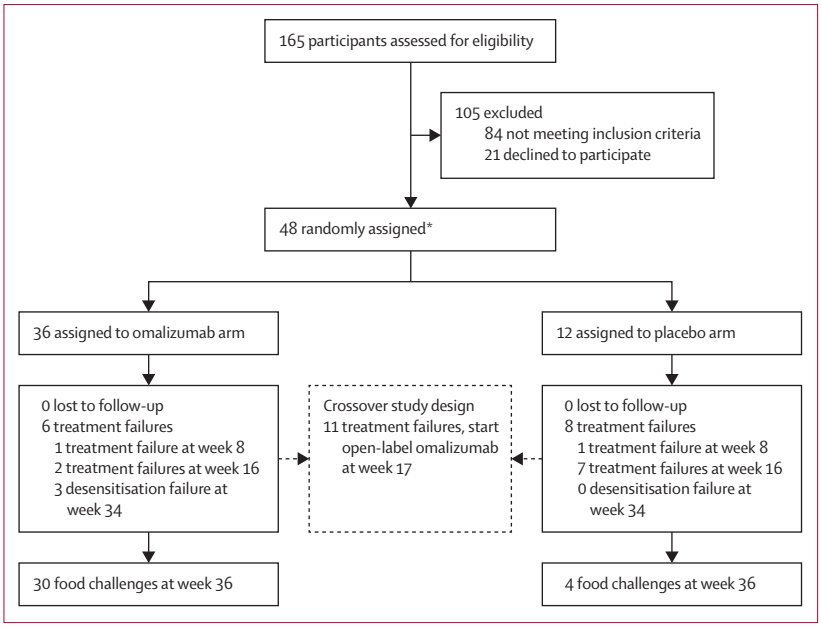

Figure 1: **Trial profile**
*12 individuals were included as non-randomised, untreated controls.

	Randomised omalizumab (n=36)	Randomised placebo (n=12)
Age (years)	8 (7·0–10·3)	7 (6·0–8·0)
Sex		
Male	18 (50%)	6 (50%)
Female	18 (50%)	6 (50%)
Hispanic ethnicity	2 (6%)	1 (8%)
History of comorbid conditions		
Asthma	16 (44%)	7 (58%)
Atopic dermatitis	28 (78%)	8 (67%)
Allergic rhinitis	26 (72%)	9 (75%)
Age at diagnosis of food allergy* (years)	1·1 (1·0–2·1)	1·7 (1·0–2·6)
Time since diagnosis of food allergy* (years)	6·3 (4·6–8·2)	5·2 (4·4–6·6)
Number of foods in oral immunotherapy	3·4 (1·1)	3·1 (1·1)
Two	10 (28%)	5 (42%)
Three	9 (25%)	2 (17%)
Four	10 (28%)	4 (33%)
Five	7 (19%)	1 (8%)
Median CTD across foods in baseline food challenge (mg)†	2·5 (0·0–5·0)	12·5 (4·4–60·0)
Total serum IgE (kU/L)	408·0 (227·5–869·1)	450·0 (253·3–585·5)
Highest specific IgE across participant's foods (kU/L)†	63·5 (20·9–90·0)	24·2 (5·8–61·7)
Median specific IgE across participant's foods (kU/L)†	13·6 (6·7–30·6)	7·1 (3·0–15·4)
Median specific IgG_4 across participant's foods (mg/L)†	0·5 (0·2–3·6)	0·7 (0·2–2·5)
Median skin prick test wheal diameter across participant's foods (mm)†	12·1 (9·4–16·8)	12·0 (8·1–16·1)

Data are n (%) or median (IQR). Number of foods in oral immunotherapy is mean (SD). CTD=cumulative tolerated dose. *Age of diagnosis per participant is determined by the median of the ages at diagnosis of the different allergies. †Only values of foods in participant's oral immunotherapy were included.

Table 1: **Demographics and immunological characteristics of the intention-to-treat population at baseline**

achieving the primary endpoint in the two study groups, with a p value of less than 0·05 considered significant. We secondarily applied an exact conditional test to compare the primary endpoint between arms after adjusting for the number of foods in the oral immunotherapy regimen per participant.

Post-hoc exploratory analyses included the time to achieve the maintenance dose of each food, and the median tolerated dose of food protein on the initial dose escalation day. We also did post-hoc sensitivity analyses by age (<8 years *vs* ≥8 years) and by the highest baseline concentration of allergen-specific IgE (<15 kU/L *vs* ≥15 kU/L).[14,15] Statistical tests, including a Wilcoxon rank sum test, Kruskal-Wallis rank sum test, log-rank test, or linear mixed-effects models, were applied for endpoint and biomarker (ie, IgE, IgG_4, skin prick test) comparisons between study arms and between baseline and week 36.

We estimated odds ratios (OR) on the basis of unconditional maximum likelihood estimation. In cases with zero cells in 2×2 tables, we used a continuity correction to obtain the OR.[16] We calculated exact confidence intervals and central Fisher's exact two-sided p values[17] using the R package exact 2×2. We used boxplots or violin plots to display the distribution of continuous variables, with each value plotted as individual dots. We connected the dots for the wheal diameters, IgE, IgG_4, and IgG_4/IgE levels per individual by a line between the violin plots for baseline and week 36. To depict the time to maintenance dose, we used a Kaplan-Meier-like approach and we estimated the hazard ratio (HR) for reaching the maintenance dose in the omalizumab group relative to the placebo group using a Cox proportional hazards regression model. Comparisons of biomarkers and clinical outcomes were adjusted for multiple comparisons by controlling the false discovery rate (FDR) to be no more than 0·05 using the Benjamini and Hochberg approach across 115 tests.

The safety analysis reported the number and proportion of participants experiencing adverse events by study period, treatment arm, and adverse event type. The safety analysis was similar to that previously published.[10]

Statistical analyses were performed using R software (version 3.4.1) and SAS (version 9.4). Most figures were created using the ggplot2 R package. This study is registered with ClinicalTrials.gov, number NCT02643862.

Role of the funding source

The main funder of the study was the NIH. Members of the NIH study team played a role in writing the clinical protocol and the manuscript as well as some study design and data interpretation, but not data collection or data analysis. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

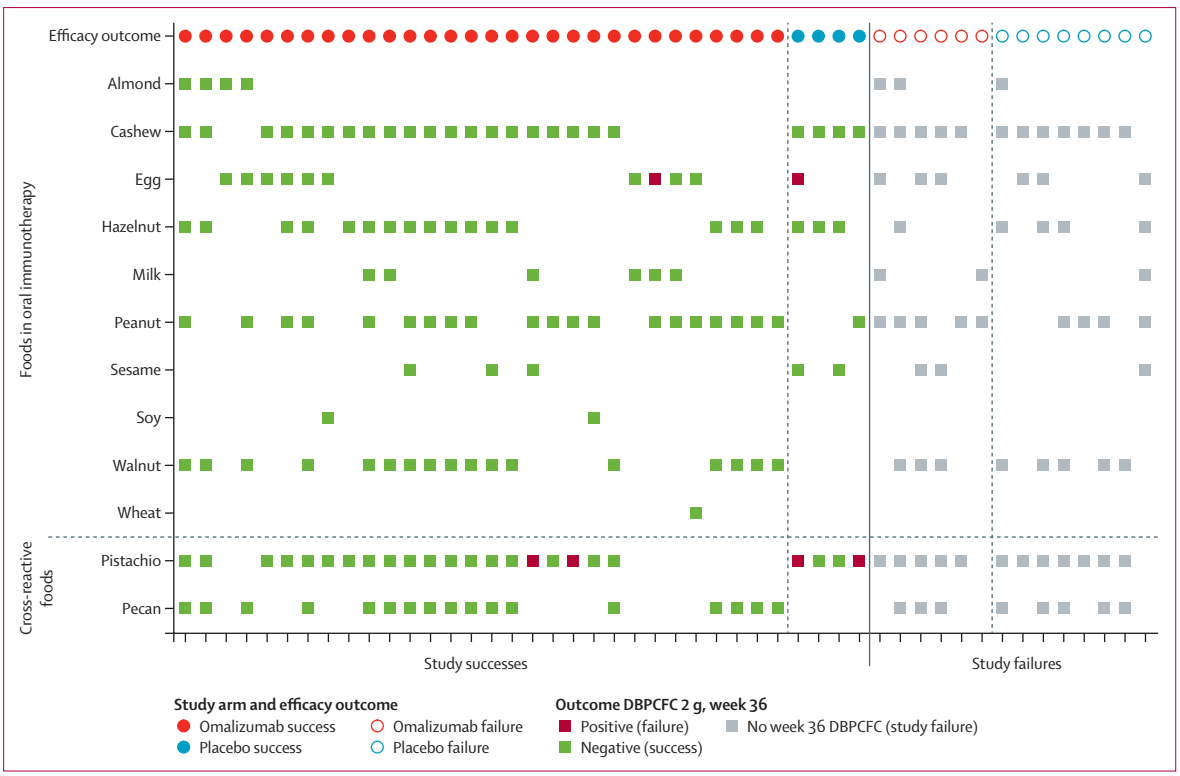

Figure 2: **Overview of foods in each participant's multifood oral immunotherapy regimen**
The outcome of the 2 g food challenge for each food in week 36 is shown in green when negative (ie, passed challenge) and in dark red when positive (ie, failed challenge). The study failures did not undergo food challenges in week 36, and the foods in their multifood oral immunotherapy regimens are indicated by grey boxes. DBPCFC=double-blind, placebo-controlled food challenge.

Results

165 participants were assessed for eligibility, of whom 84 did not meet the inclusion criteria and 21 declined to participate (figure 1). We enrolled 48 eligible participants, aged 4–15 years, and randomised 36 to receive omalizumab and 12 to receive placebo. A further group of 12 individuals were included as non-randomised, untreated controls. All enrolled participants finished the study and were included in the ITT analysis for the primary endpoint. The 48 enrolled participants had similar demographic and immunological characteristics (table 1, appendix p 21). Two (n=10 for omalizumab group *vs* n=5 for placebo), three (n=9 *vs* n=2), four (n=10 *vs* n=4), or five (n=7 *vs* n=1) foods were included in the oral immunotherapy regimens. The mean number of foods per participant included in the oral immunotherapy regimens was 3·4 (SD 1·1) for the omalizumab group and 3·1 (1·1) for the placebo group. At the baseline food challenge, the median cumulative tolerated dose of food protein per food was 2·5 mg (IQR 0·0–5·0) for the omalizumab group and 12·5 mg (4·4–60·0) for the placebo group (table 1).

Figure 2 shows the combinations of foods in each participant's multifood oral immunotherapy regimen, and their success (negative challenge) or failure (positive challenge) in passing the week 36 food challenges to 2 g of the relevant foods. The combinations of foods in the separate participants' oral immunotherapy regimens were substantially diverse (as presented in Andorf and colleagues[18]).

In the ITT analysis, 30 (83%) of 36 participants in the omalizumab group versus four (33%) of 12 participants in the placebo group passed the week 36 food challenge to 2 g of each of two foods (or more) in their multifood oral immunotherapy regimen (OR 10·0, 95% CI 1·8–58·3, p=0·0044, table 2, appendix p 6). Differences in the proportion of individuals who passed at least two food challenges between the two groups remained significant after stratifying by the number of foods in participants' multifood oral immunotherapy regimen (p=0·0016; table 2). With the exception of two participants, all of those who achieved the primary endpoint passed food challenges to all of the offending foods included in their oral immunotherapy regimen. One participant from each group failed the food challenge to egg at week 36 (figure 2). Every participant who tolerated 2 g of at least two foods in the week 36 food challenges also tolerated 4 g for at least two foods in the same challenges (OR 10·0, 95% CI 1·8–58·3; p=0·0044, appendix p 6).

A significantly larger proportion of participants in the omalizumab group also achieved the secondary efficacy endpoints of passing food challenges to 2 g of each of

	Omalizumab (n=36)	Placebo (n=12)	OR* (95% CI)	p value (adjusted†)
Tolerated 2 g of at least two foods‡				
Total	30/36 (83%)	4/12 (33%)	10·0 (1·8–58·3)	0·0044 (0·0016)
Two foods in OIT	8/10 (80%)	2/5 (40%)	..	..
Three foods in OIT	9/9 (100%)	1/2 (50%)	..	..
Four foods in OIT	9/10 (90%)	1/4 (25%)	..	..
Five foods in OIT	4/7 (57%)	0/1 (0%)	..	..
Tolerated 2 g of at least three foods‡				
Total	21/26 (81%)	2/7 (29%)	10·5 (1·2–128·6)	0·032 (0·010)
Three foods in OIT	8/9 (89%)	1/2 (50%)	..	..
Four foods in OIT	9/10 (90%)	1/4 (25%)	..	..
Five foods in OIT	4/7 (57%)	0/1 (0%)	..	..
Tolerated 2 g of at least four foods‡				
Total	13/17 (76%)	0/5 (0%)	33 (1·9–not reached)	0·0096 (0·0025)
Four foods in OIT	9/10 (90%)	0/4 (0%)	..	
Five foods in OIT	4/7 (57%)	0/1 (0%)	..	..
Tolerated 2 g of five foods‡				
Five foods in OIT (total)	4/7 (57%)	0/1 (0%)	3·9 (0·03–not reached)	1

OR=odds ratio. OIT=oral immunotherapy. *ORs were estimated based on unconditional maximum likelihood estimation. In cases with zero cells in 2 × 2 tables, a continuity correction was used to obtain the OR.[16] †p value for the indicated endpoint after adjusting for the number of foods in the oral immunotherapy regimen per participant. ‡n of participants who achieved that endpoint/n of participants with the indicated number of foods in their oral immunotherapy (%).

Table 2: **Efficacy outcomes for primary endpoint and major secondary endpoints**

three, four, or five foods compared with the placebo group (table 2). In the omalizumab group, 21 (81%) of 26 individuals with three or more foods in their multifood oral immunotherapy tolerated 2 g of at least three foods at week 36 compared with only two (29%) of seven participants in the placebo group. The OR for passing challenges to at least three foods in the omalizumab group versus placebo group was 10·5 (95% CI 1·2–128·6; p=0·032; table 2). The differences between the study groups remained significant (p=0·010) after the data were adjusted for the number of foods in each of the participants' oral immunotherapy regimens. Similarly, in the omalizumab group, 13 (76%) of 17 individuals with four or five foods in their oral immunotherapy regimens tolerated 2 g of at least four foods at week 36 compared with none of the five participants in the placebo group (table 2); similar results were noted in individuals with five foods included in their oral immunotherapy regimen (table 2).

There were no serious adverse events (defined as per ICH/CFR FDA-GCP guidelines) nor any severe ones (grade 3 according to the NCI-CTCAE system; table 3). We designed the protocol to take advantage of the potential safety enhancement afforded by anti-IgE blockade. During weeks 8–16, the period that allowed a straightforward assessment of drug benefit on oral immunotherapy safety, all participants experienced at least one adverse event; however, those in the omalizumab group had a significantly lower median per-participant percentage of oral immunotherapy doses associated with any adverse events compared with those in the placebo group (27% *vs* 68%; p=0·0082; table 3), whereas adverse events were similar between the groups at later times (table 3). Gastrointestinal and respiratory adverse events have been associated with early terminations, severe reactions, and non-compliance in oral immunotherapy studies.[1,3,4] Those on omalizumab experienced a significantly lower median per-participant percentage of oral immunotherapy doses associated with gastrointestinal adverse events (22% *vs* 54%; p=0·044) and respiratory adverse events (0% *vs* 1%, p=0·023; table 3). Individuals who failed treatment started open-label omalizumab with oral immunotherapy after week 16 (listed separately in table 3). Adverse events did not increase in the 33 individuals in the omalizumab group after omalizumab withdrawal at week 16 (table 3). Secondary safety outcomes did not differ significantly between groups (appendix p 22). Analysis of treatment for adverse events and injectable epinephrine use for each participant is detailed in the appendix (pp 4, 23). We found no significant associations between safety parameters and various participant characteristics (appendix p 24) or between percentage of oral immunotherapy doses associated with adverse events and success outcomes (appendix p 7).

Maintenance was achieved as early as 12 weeks in the omalizumab group versus 20 weeks in the placebo group. The time to achieve the maintenance dose for each food was less in the omalizumab versus the placebo group (p=0·0011, FDR adjusted p=0·0055; HR for reaching the maintenance dose [omalizumab *vs* placebo] was 5·36, 95% CI 1·8–15·99; figure 3). For participants receiving omalizumab there was a trend toward a delay in achieving the maintenance dose per food with increased number of foods in the oral immunotherapy regimen (p=0·033, FDR adjusted p=0·10, figure 3 and appendix p 8).

The median tolerated dose on the initial dose escalation day at week 8 was significantly greater for participants receiving omalizumab than for those in the placebo group (250 mg per food [1250 mg median total dose, the maximum tested] *vs* 11 mg per food [50 mg median total dose], p<0·0001, FDR adjusted p<0·0001; appendix p 9). Individuals who achieved the primary endpoint in the omalizumab group tolerated a greater dose per food at the initial dose escalation day compared with study failures (p=0·014, FDR adjusted p=0·055, appendix p 9); this difference was not detected for the placebo arm (p=0·49, FDR adjusted p=0·69, appendix p 9). The same outcomes hold true for the total tolerated dose at initial dose escalation day.

For participants younger than 8 years, we did not observe a statistically significant difference between groups in the primary outcome (OR 3·0, 95% CI 0·3–30·2; p=0·50, FDR adjusted p=0·69; table 4). In the older (≥8 years) participants, however, a greater proportion of participants in the omalizumab group

	Participants with adverse event (n)	Any adverse event	Gastrointestinal	General*	Respiratory	Skin	Other†	Treated	Grade 1	Grade 2	p value‡
Weeks 8–16§¶											
Omalizumab	36	27 (4–67)	22 (0–43)	0 (0–0)	0 (0–0)	0 (0–2)	0 (0–0)	3 (1–20)	25 (2–48)	2 (0–12)	0·0082
Placebo	12	68 (51–93)	54 (19–76)	0 (0–8)	1 (0–9)	0 (0–5)	0 (0–0)	28 (12–47)	56 (46–70)	7 (1–20)	..
p value‖	..	..	0·044	..	0·023	..	..	..	..	..	..
Weeks 17–24											
Omalizumab¶	33	26 (0–57)	20 (0–50)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–2)	22 (0–50)	0 (0–0)	0·37
Placebo¶	4	39 (20–68)	24 (0–50)	0 (0–1)	4 (0–20)	4 (2–15)	0 (0–0)	33 (7–53)	39 (16–68)	0 (0–4)	..
Omalizumab§** (treatment failures)	3	100 (26–100)	26 (0–100)	0 (0–0)	0 (0–0)	0 (0–100)	0 (0–0)	33 (0–100)	26 (0–67)	33 (0–100)	NA
Placebo§** (treatment failures)	7	27 (0–41)	25 (0–41)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–2)	0 (0–29)	0 (0–0)	..
Weeks 25–36											
Omalizumab¶	33	29 (1–55)	13 (0–33)	0 (0–0)	0 (0–2)	0 (0–8)	0 (0–0)	5 (0–23)	16 (0–41)	0 (0–8)	0·56
Placebo¶	4	29 (17–54)	11 (5–20)	7 (1–14)	1 (0–9)	1 (0–24)	0 (0–0)	16 (9–39)	28 (17–42)	1 (0–12)	..
Omalizumab§¶†† (treatment failures)	3	12 (0–26)	0 (0–21)	2 (0–12)	0 (0–4)	0 (0–0)	0 (0–0)	9 (0–12)	12 (0–23)	0 (0–4)	NA
Placebo§¶†† (treatment failures)	8	19 (0–30)	7 (0–23)	0 (0–0)	0 (0–17)	0 (0–0)	0 (0–0)	0 (0–18)	19 (0–30)	0 (0–0)	..

Data are n (%) and median (IQR) per-participant percentage of doses where an adverse event occurred by week and treatment arm. The adverse events reported in the table are associated with multifood oral immunotherapy. There were no grade 3 events. Three of the study failures in the omalizumab group were desensitisation failures and were therefore included in the general omalizumab group for the safety assessment for weeks 17–24 and 25–36. *General indicates skin reactions at injection site. †Other indicates anxiety or eye reactions. ‡Based on Wilcoxon rank sum test comparing any adverse event between omalizumab and placebo. §Study drug administered (placebo or omalizumab). ¶Multifood oral immunotherapy administered. ‖p values shown when less than 0·05. **Initial dose escalation day for participants on open-label omalizumab with oral immunotherapy included. ††Omalizumab in open-label was administered from week 17 to week 32. NA=not applicable (insufficient participants to calculate p value).

Table 3: **Safety summary**

achieved the primary outcome compared with the placebo group (OR 42·0, 95% CI 2·1–2117·2; p=0·0068, FDR adjusted p=0·028). For the group with the highest allergen-specific IgE of 15 kU/L or more at baseline, administration of omalizumab resulted in a significantly greater success rate than in the placebo group (OR 30·0, 95% CI 2·5–1417·6; p=0·0024, FDR adjusted p=0·011 table 4); no statistically significant treatment effect was seen in the group with baseline highest allergen-specific IgE less than 15 kU/L, but the sample size was small.

A trend towards a higher rate of success with increased age was seen, independent of the study group (p=0·041, FDR adjusted p=0·12; appendix p 25). Only a greater tolerated dose at initial dose escalation day per bodyweight was significantly associated with study success after FDR adjustment (appendix p 25). Furthermore, the highest of the specific IgE values at baseline to any of the foods in the participants' oral immunotherapy showed a trend to be important for the study outcome in the placebo group (p=0·072, FDR adjusted p=0·19, appendix p 10), while this was not the case in the omalizumab group. Additionally, the median of the cumulative tolerated doses at baseline food challenge to all foods in the participant's multifood oral immunotherapy (appendix p 11) was not significantly different within one arm between study successes and failures, but it shows (given the small sample size) the trend that placebo failures tended to tolerate lower cumulative tolerated doses at baseline.

In all study successes, specific IgG_4/IgE ratios significantly increased between baseline and week 36 for most foods, primarily reflecting increases in IgG_4 rather than changes in IgE (appendix pp 12–14). Treatment successes for most foods were also associated with a significant decrease in skin prick test wheal diameters between baseline and week 36 (appendix p 18). However, none of the six study successes in the omalizumab group, whose multifood oral immunotherapy included milk, exhibited significant changes in either specific IgG_4/IgE ratios (appendix p 14) or skin prick test wheal diameters (appendix p 18) for milk, despite passing the food challenge for milk. The untreated, non-randomised controls showed no significant change in levels of specific IgE or specific IgG_4, ratios of specific IgG_4/specific IgE, or skin prick test results for any food over the same time span of 36 weeks (appendix pp 15–17, 19).

Possible cross-desensitisation was tested in 24 individuals with both pistachio and cashew allergies and in 17 participants with both pecan and walnut allergies who were successfully desensitised to cashew, walnut, or both. For individuals whose oral immunotherapy regimen included cashew, 83% also passed a food challenge with pistachio at week 36; all of those whose oral immunotherapy regimens included walnut passed a food challenge with pecan at week 36 (figure 2 and appendix p 20).

Discussion

Omalizumab treatment for 16 weeks combined with multifood oral immunotherapy is safe and allows for improved multifood desensitisation compared with multifood oral immunotherapy combined with placebo,

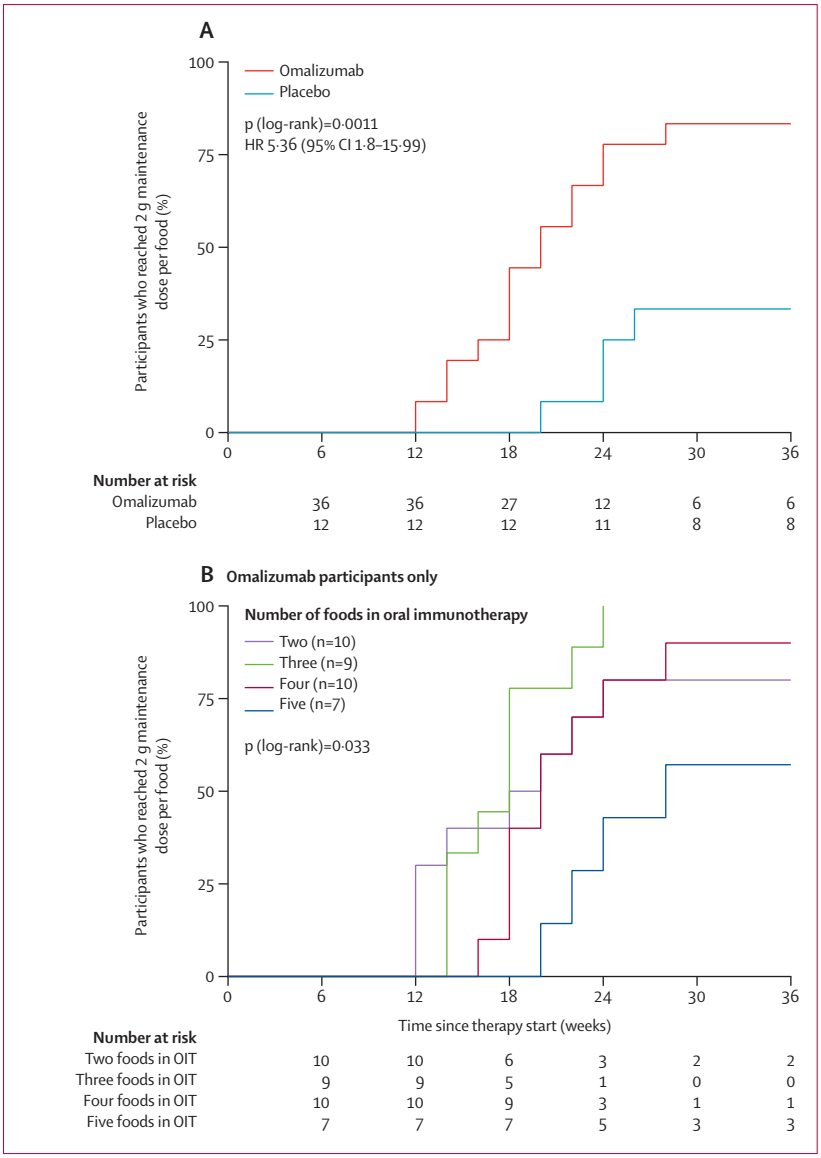

Figure 3: **Time since starting therapy to reach a 2 g maintenance dose per food**
(A) Time since starting therapy (omalizumab or placebo) for participants to reach a 2 g maintenance dose per food and (B) stratified by the number of foods in the participant's multifood oral immunotherapy. Study failures (six in the omalizumab arm, eight in the placebo arm) who never reached 2 g maintenance were censored at week 36. OIT=oral immunotherapy. HR=hazard ratio.

	Omalizumab	Placebo	OR (95% CI)	p value	FDR-adjusted p value
Age (years)					
<8	9/13 (69%)	3/7 (43%)	3·0 (0·3–30·2)	0·50	0·69
≥8	21/23 (91%)	1/5 (20%)	42·0 (2·1–2117·2)	0·0068	0·028
Highest baseline specific IgE (kU/L)					
<15	5/6 (83%)	3/5 (60%)	3·3 (0·1–234·8)	0·85	0·92
≥15	25/30 (83%)	1/7 (14%)	30·0 (2·5–1417·6)	0·0024	0·011

n successfully achieved primary endpoint/n with that characteristic (%). Highest specific IgE value at baseline against any of the foods included in that participant's multifood oral immunotherapy regimen. FDR=false discovery rate. OR=odds ratio.

Table 4: **Highest allergen-specific IgE and age by primary efficacy outcome**

as shown by the reduced adverse events during the build-up phase, and increased ability to pass a food challenge with 2 g each of at least two offending foods at week 36. This phase 2 clinical trial thus shows the potential benefits of using omalizumab to facilitate multifood desensitisation to a variety of food allergens in a shortened period of time. Multiple food allergies affect a significant proportion of people with food allergies worldwide, and these patients can have allergic reactions after ingesting any of several different offending foods.[1] Although no oral immunotherapy is currently approved for treatment of single food allergies, let alone for multiple food allergies, multiallergen immunotherapy for environmental allergies is routine.[19] Attempting to treat individuals with multifood allergies with sequential single oral immunotherapy to each of their offending foods would result in many years of treatment. Omalizumab has been shown to be useful in single food oral immunotherapy and in shortening the time course of desensitisation, as recently reviewed by Lin and colleagues.[20] Additionally, our group performed a small pilot phase 1 study combining multifood oral immunotherapy with omalizumab treatment, which showed feasibility and tolerability of dosing multifood oral immunotherapy using omalizumab as an adjunct therapy.[2] Therefore, we designed this randomised, controlled phase 2 study using initial omalizumab dosing to test the safety and efficacy of rapid multifood oral immunotherapy.

This finding provides evidence that, in multifood oral immunotherapy, as with single food oral immunotherapy,[21–26] this strategy can be successful in such individuals. Our population showed evidence of a high level of clinical reactivity, including high levels of food allergen-specific IgE, and reactions at relatively low cumulative doses of offending foods (≤500 mg of protein to each food) at baseline food challenge.

The efficacy data from this study are at least comparable to those reported for single food oral immunotherapy without omalizumab[3] and therefore would suggest that the overall effectiveness of oral immunotherapy (with omalizumab) is not reduced with increased numbers of foods.

We chose 2 g for the primary endpoint because many multifood allergic patients have milk or egg allergies for which a 2 g accidental ingestion is common.[27] The ability to tolerate 2 g for at least two foods was also achieved in individuals with allergies to three, four, or five offending foods. Furthermore, the same participants who met the primary endpoint of 2 g also tolerated 4 g for at least two of the foods in the food challenge at 36 weeks. For many of these food proteins, 4 g represents an average serving (eg, about one tablespoon of peanut butter), and the ability to increase an individual's threshold of food ingestion to a serving of protein is important for their nutrition and overall quality of life.[28] Those in the omalizumab group also required

substantially shorter times to reach the maintenance dose of 2 g of each food compared with those in the placebo group, thus potentially improving the chances of adherence since many individuals drop out of clinical oral immunotherapy studies in the first 3–6 months.[23–25,29] This compressed timing is another advantage conferred by omalizumab, because it suggests that less frequent visits for updosing would be required, a potentially important consideration in school-aged children and working adults. Our data show that oral immunotherapy-induced protection was evident at least 20 weeks after stopping the 16 week course of omalizumab therapy. The 36 week timepoint for the primary and secondary efficacy endpoints was chosen to allow for several omalizumab half-lives to pass; however, we cannot formally conclude that there was no residual effect of omalizumab treatment at 36 weeks. A potential concern with using omalizumab is that participants might be at risk for allergic reactions once omalizumab treatment is stopped; however, our data showed no increased frequencies of adverse events after discontinuation of omalizumab and no increased frequency of adverse events during omalizumab treatment.

However, there were significant differences in safety outcomes between the two study groups during weeks 8–16, notably decreased gastrointestinal and respiratory symptoms in the omalizumab group. This improvement in safety with omalizumab is a crucial aspect of our protocol. Indeed, we expected that omalizumab would effectively enable us to reach higher doses of food protein faster because of incremental safety improvements.[2,9,10] Minimising adverse events during updosing might also enhance long-term compliance. Finally, we found evidence of possible cross-desensitisation in individuals with pistachio and cashew allergies or pecan and walnut allergies when they only ingested one of each (cashew or walnut) in the oral immunotherapy regimen, but further work will be needed to identify the mechanism(s) underlying these findings.

Our study has limitations. The interpretation of the safety data between omalizumab-treated versus placebo-treated participants after week 16 is challenging because we included in the safety assessment participants that failed treatment and started open-label omalizumab at week 17. However, we anticipated that this design would encourage participant adherence, and indeed this might have contributed to the fact that no-one dropped out of the study. In this small study of limited duration, we did not do basophil assays (which would have required additional blood for testing), and we did not measure total IgE over time, including at 36 weeks. Some current evidence indicates that total IgE is still being studied for its use in food allergy.[30–32] We only measured total IgE at baseline to follow the product insert for omalizumab dosing. In future studies, it would be interesting to examine ratios of various biomarkers to total IgE to determine if they predict outcomes of oral food challenges. Furthermore, we did not test sustained unresponsiveness, which will be the focus of a future trial. Finally, we assume that omalizumab speeds up the process of desensitisation by decreasing the threshold of reactivity of effector cells. We are continuing to pursue other phase 2 trials to answer the question of whether the placebo participants would benefit from oral immunotherapy if carried out for a longer period of time.

In conclusion, our results suggest that multifood oral immunotherapy in combination with a short initial course of omalizumab (16 weeks) will permit effective desensitisation to be achieved rapidly in the majority of multifood allergic participants.

Contributors

SA collected data, did the statistical analyses, created figures and tables, and wrote the manuscript. NP collected safety data, did the safety statistical analysis, and created the safety tables. WMB collected data and conducted clinical aspects of the study. AJL collected data and contributed to the study. DT collected data. EB provided advice on the statistical analysis plan for protocol, helped to interpret the data, and wrote the manuscript. ARS helped to design the study protocol, to interpret data, and to write the manuscript. MD oversaw the statistical analysis. SJG oversaw the study as part of the NIAID Asthma and Allergic Diseases Cooperative Research Center (AADCRC; as principal investigator), helped in study design and data interpretation, and wrote the manuscript. KCN designed and conducted the study, interpreted the data, and wrote the manuscript. RSC helped in study design and conducted the study, interpreted the data and wrote the manuscript. All authors reviewed and approved the manuscript.

Declaration of interests

SA reports grants from NIH, during the conduct of the study. WMB reports grants from NIH, during the conduct of the study. SJG reports grants from NIAID, during the conduct of the study; grants from NIH, outside the submitted work; and is an author of manuscripts discussing the use of personalised medicine in treatment of allergic diseases. KCN reports grants from NIH; non-financial support from Genentech; personal fees from Novartis; and sponsored research from AnaptysBio, AImmune, DBV Biosciences, and Astellas, outside the submitted work. RSC reports grants from NIAID, during the conduct of the study; grants and fees for serving on an advisory board from Aimmune Therapeutics and grants from DBV Technologies, AnaptysBio, and Astellas Pharma Global Development, outside the submitted work. All other authors declare no competing interests.

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Food allergy: setting the scene for tolerance induction

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IgE-mediated food allergies seem to have increased dramatically in the last few decades.[1,2] This increase is often referred to as the second allergy wave, because it follows the observed rise of allergies of the upper and lower airways (ie, allergic rhinoconjunctivitis and asthma) that started in the 1960s. The current food allergy epidemic appears to be a perfect storm involving an increased prevalence of sensitised children, an increased severity profile, and a broadening of reactivity from fewer to more allergenic foods, although the most prevalent in infancy are still milk and egg, followed by peanut and tree nuts in young children, and fish, crustaceans, seeds, and cereals in older children and adults.

Interesting results have been obtained in the field of primary prevention of peanut allergy in infants,[3] but data are less convincing for other age groups and allergenic foods,[4] and a cure for an established food allergic disease is still not available. Pharmacological control of asthma and hayfever might reduce the risk of severe reactions upon ingestion of a culprit food in a given individual, but classic anti-allergic drugs are by no means preventive. Inspired by the relative success of allergen immunotherapy for attenuation of symptoms in inhalation allergies—induced by allergens such as grass and birch pollen and house dust mites—a similar approach has been tested in food allergies. In view of the vigorous acute response of a food allergic individual to food proteins, various strategies to eliminate allergic side-effects have been tested, such as creation of hypoallergenic molecules[5] or use of routes of administration[1] other than the subcutaneous route that is predominantly used in allergen immunotherapy for allergic airway diseases. In this respect, an oral form of immunotherapy, in which individuals ingest daily dosages of food proteins with gradual dose increases have been described[1,6] and shown to be efficient, safe, and patient-friendly. In spite of some success, however, oral immunotherapy is still likely to produce allergic side-effects during up-dosing, and the Achilles' heel of the treatment is its sustainability. It remains unclear whether oral immunotherapy-induced tolerance will endure when daily dosing is stopped for a period.

In *The Lancet Gastroenterology & Hepatology*, Sandra Andorf and colleagues[7] present a clinical trial in the most vulnerable food allergic patients, namely those with not just a single, but multiple food allergies. By including participants with a high level of sensitisation (large skin prick test areas, high levels of food-specific IgE in serum, or both) the study addresses the most severely affected and thus difficult-to-treat part of the food allergic population. The purpose of the study was to determine whether oral immunotherapy is possible in this group if given under a cover of omalizumab, a humanised antibody that neutralises circulating IgE and is assumed to gradually reduce mast cell-bound IgE and thus the allergic reactivity of the patient. In the trial, an omalizumab (or placebo) pretreatment period of 8 weeks was used before initiating the oral immunotherapy. The primary outcome was the proportion of participants who passed a titrated double-blinded, placebo-controlled food challenge to 2 g of food protein (per food)—the gold standard of food allergy diagnosis.

The good news is that the anti-IgE cover conferred a much improved safety profile on the multiple-food oral immunotherapy, and this allowed for a higher success rate in the patients who received omalizumab pretreatment compared with those who received placebo. For these individuals, failing to pass the placebo-controlled food challenge is much less of a problem than is not being able to adhere to the dosage schedule due to adverse events. The trial was a phase 2 study, and it could be argued that with a less aggressive dose-increment schedule fewer patients would have experienced side-effects and thus would have been able to reach tolerance. However, as several oral immunotherapy studies have shown, some patients might never be able to tolerate more than a specific dose of food protein. Considering the safety of the patients and the costs of this treatment to the health-care system, iterative adjustments and readjustments of dosage schedules are unlikely to lead to success in such highly vulnerable patients who are afflicted by multiple food hypersensitivities.

As discussed by the authors, the study has limitations. Whether tolerance was sustained was not addressed, and this question will require future studies. Furthermore, not all patients can be treated adequately with omalizumab due to very high levels of serum IgE, and this might in particular cause problems in the substantial subset of patients with atopic dermatitis, a condition often seen in conjunction with food allergy.

On the other hand, new molecules targeting IgE are in the pipeline that might further improve the anti-IgE cover. One might question whether cumbersome oral immunotherapy is necessary if anti-IgE does the trick. But as the study by Andorf and colleagues shows, a careful dose increase of the culprit allergenic food is still necessary to induce tolerance. This makes the situation complex, and one can only hope that this study will inspire more incremental research in the optimal dose–time relationships necessary for not only reaching temporary tolerance immediately after the treatment period, but also a sustained endurance.

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