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Omalizumab for the Treatment of Multiple Food Allergies

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Abstract

BACKGROUND—Food allergies are common and are associated with substantial morbidity; the only approved treatment is oral immunotherapy for peanut allergy.

METHODS—In this trial, we assessed whether omalizumab, a monoclonal anti-IgE antibody, would be effective and safe as monotherapy in patients with multiple food allergies. Persons 1 to 55 years of age who were allergic to peanuts and at least two other trial-specified foods (cashew, milk, egg, walnut, wheat, and hazelnut) were screened. Inclusion required a reaction to a food challenge of 100 mg or less of peanut protein and 300 mg or less of the two other foods. Participants were randomly assigned, in a 2:1 ratio, to receive omalizumab or placebo administered subcutaneously (with the dose based on weight and IgE levels) every 2 to 4 weeks for 16 to 20 weeks, after which the challenges were repeated. The primary end point was ingestion of peanut protein in a single dose of 600 mg or more without dose-limiting symptoms. The three key secondary end points were the consumption of cashew, of milk, and of egg in single doses of at least 1000 mg each without dose-limiting symptoms. The first 60 participants (59 of whom were children or adolescents) who completed this first stage were enrolled in a 24-week open-label extension.

RESULTS—Of the 462 persons who were screened, 180 underwent randomization. The analysis population consisted of the 177 children and adolescents (1 to 17 years of age). A total of 79 of the 118 participants (67%) receiving omalizumab met the primary end-point criteria, as compared with 4 of the 59 participants (7%) receiving placebo (P<0.001). Results for the key secondary end points were consistent with those of the primary end point (cashew, 41% vs. 3%; milk, 66% vs. 10%; egg, 67% vs. 0%; P<0.001 for all comparisons). Safety end points did not differ between the groups, aside from more injection-site reactions in the omalizumab group.

CONCLUSIONS—In persons as young as 1 year of age with multiple food allergies, omalizumab treatment for 16 weeks was superior to placebo in increasing the reaction threshold for peanut and other common food allergens. (Funded by the National Institute of Allergy and Infectious Diseases and others; ClinicalTrials.gov number, NCT03881696.)

Food allergy affects up to 8% of children and 10% of adults in the United States,[1,2] and a large percentage (30 to 86%) of affected persons are allergic to multiple foods.[3,4] Living with food allergy requires constant vigilance and has detrimental effects on nutrition, quality of life, personal finances, and health care utilization.[5,6] Current management recommendations rely on food avoidance and emergency treatment if accidental exposure occurs. Only one treatment has been approved by the Food and Drug Administration, an oral immunotherapy product for peanut allergy.[7] Although oral immunotherapy has been shown to induce desensitization to specific food allergens, it is a burdensome therapy associated with a high incidence of adverse reactions.[8,9] The development of therapeutic strategies that could address allergies to multiple foods simultaneously, reduce reactions to accidental exposures, and improve overall quality of life would be an important advance for affected persons.

Omalizumab, a monoclonal antibody that binds to IgE, has shown promise for the treatment of food allergy in numerous small trials.[8,10–17] It is currently approved for treatment of allergic asthma in children as young as 6 years of age and for chronic spontaneous urticaria and chronic rhinosinusitis with nasal polyps in adolescents and adults. Studies have shown that omalizumab and other anti-IgE therapies increase the threshold of reactivity to foods when given alone, and when given with oral immunotherapy, can reduce the incidence and severity of adverse events and decrease the time needed for dose escalation.[8,10–18] The Omalizumab as Monotherapy and as Adjunct Therapy to Multi-Allergen Oral Immunotherapy (OIT) in Food Allergic Children and Adults (OUtMATCH) trial was designed as a phase 3 trial to more fully evaluate the safety and efficacy of omalizumab as a treatment that blocks immune responses irrespective of antigen type for patients as young as 1 year of age who are allergic to multiple foods.

METHODS

TRIAL DESIGN AND OVERSIGHT

OUtMATCH is a double-blind, randomized, placebo-controlled trial that is being conducted at 10 centers in the United States. The trial methods have been published,[19] and the protocol and statistical analysis plan are available with the full text of this article at NEJM.org. The trial includes three stages, but only the first stage, a direct comparison of omalizumab

with placebo, has been completed and is reported here. The second stage will compare longer-term (52 weeks) treatment with omalizumab with oral immunotherapy for multiple food allergies, and the third stage will assess the introduction of allergenic foods into the diet for ongoing consumption (minimum, 52 weeks) at home after discontinuation of treatment with omalizumab or oral immunotherapy.

The protocol was designed by the authors, including the investigators of the Consortium for Food Allergy Research and representatives from the National Institute of Allergy and Infectious Diseases, Genentech, Novartis, and Rho. Genentech and Novartis provided the investigational product and monetary support to Johns Hopkins University and collaborated on the trial design. The trial was approved by a central institutional review board at Johns Hopkins University, conducted under an investigational new drug application (number 140847), and monitored by an independent data and safety monitoring board. Trial data were collected by the investigators and analyzed at the coordinating center (Rho). The manuscript was drafted by the first author, and all the authors had access to and participated in the interpretation of the data and provided input into the preparation and submission of the manuscript. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

TRIAL PARTICIPANTS

Persons 1 to 55 years of age with a history of allergy to peanut and at least two other foods in the protocol-specified list (cashew, milk, egg, walnut, wheat, and hazelnut) were screened. If the results of skin-prick and laboratory testing confirmed the food allergies, double-blind, placebo-controlled oral food challenges followed. Each food challenge was given in gradually increasing doses administered at 15-to-30-minute intervals. Eligibility required dose-limiting symptoms, as defined by the Consortium for Food Allergy Research grading scale for acute allergic reactions,[20] after a single dose of 100 mg or less of peanut protein (cumulative amount ingested, 144 mg) and 300 mg or less of the other allergens in the list (cumulative, 444 mg) (see Table S1 in the Supplementary Appendix, available at NEJM.org) and a negative placebo (oat) challenge.[21] Inclusion also required a body weight and serum IgE level suitable for omalizumab dosing according to a modified dosing algorithm for asthma (Fig. S1). Key exclusion criteria were poorly controlled or severe asthma, a history of severe anaphylaxis (defined as anaphylaxis resulting in neurologic compromise or intubation) to participant-specific foods, previous immunotherapy for any of the protocol-specified foods, or monoclonal antibody therapy within 6 months before screening.

RANDOMIZATION AND ENROLLMENT

Participants underwent randomization, in a 2:1 ratio, to receive omalizumab or placebo, administered subcutaneously, every 2 to 4 weeks for a total of 16 to 20 weeks, at the doses and frequency indicated on the trial dosing table, which were based on weight and total IgE levels (Fig. S1); this period was followed by a repetition of the four food challenges (three allergens plus placebo) over a period of up to 4 weeks, during which injections were continued. The first 60 participants who completed this stage of the trial were enrolled in a 24-week open-label extension, followed by another four food challenges, to further assess

the safety and durability of response (Fig. S4). During both the first stage of the trial and the open-label extension, participants were instructed to continue to avoid their food allergens.

In addition, because enrollment was slowed by the coronavirus disease 2019 (Covid-19) pandemic and we believed that omalizumab might provide an important treatment option for persons with food allergies, we conducted an interim analysis of the primary and key secondary end points. In this analysis involving 165 children and adolescents, omalizumab would be declared effective only if the two-sided P value for the comparison with respect to peanut, performed with Fisher's exact test, would be significant at $P<0.0001$ and if the P value for the comparison with respect to cashew, egg, and milk would be significant at $P<0.005$ for all comparisons. The analysis showed that the direction of all four differences between groups favored omalizumab, so we ended the period of enrollment with a final sample size of 177 children and adolescents instead of the planned enrollment of 210 (a total of 180 pediatric and adult participants enrolled instead of the 225 originally planned).

END POINTS

The primary end point was consumption of a single dose of at least 600 mg of peanut protein without dose-limiting symptoms at the completion of the first stage of the trial. The three key secondary end points that were protocol-specified and included in the plan to adjust for multiple comparisons were the consumption of cashew, of milk, and of egg protein in single doses of at least 1000 mg each without dose-limiting symptoms. For the primary and key secondary end points, if a participant who underwent randomization did not complete a food challenge for any reason, the participant was considered not to have met the efficacy end points (i.e., imputation of failure). Therefore, there are no missing data for these end points: of the 14 missing food challenges for which failure was imputed, 13 were in the omalizumab group.

Other secondary end points included consumption in escalating doses up to 4000 mg of a single food, of at least two foods, and of all three foods without dose-limiting symptoms; and the number of foods consumed at various doses (one dose of ≥600 mg or ≥1000 mg, at least one dose of 2000 mg, or two doses of 2000 mg) without dose-limiting symptoms. Additional end points included quality of life, safety, skin-prick testing, and basophil-activation testing, as well as the same end points after the open-label extension. All adverse events possibly related to trial procedures or products were recorded and reported as detailed in the protocol and in the Methods section in the Supplementary Appendix.

STATISTICAL ANALYSIS

For the primary analysis of the primary and key secondary end points, we used a two-sided Fisher's exact test to compare the two groups with respect to the percentage of the participants who consumed the target food dose without dose-limiting symptoms. To handle issues of multiplicity, we used gatekeeping and sequential testing strategies to ensure that the overall family-wise two-sided error rate would be below 0.05 for the primary and three key secondary end points between the planned interim analysis and the possible final analysis (if the interim analysis was not successful). Enrollment was stopped after the interim analysis, which was reviewed and approved by the independent data and safety monitoring board,

showed efficacy (Table S4). Additional statistical methods and power analyses are shown in the Supplementary Appendix, including Tables S5A and S5B. Secondary end points that were not included in the plan to adjust for multiple testing results are reported with 95% confidence intervals, without P values; the 95% confidence intervals have not been adjusted for multiple testing and should not be used to infer treatment effects. Because the pediatric population was the prespecified primary analysis population, results reported here are for that population only (details of the three adult participants are provided in Tables S12A through S12E).

RESULTS

PARTICIPANTS

A total of 435 children and adolescents were screened, of whom 177 underwent randomization from September 2019 through November 2022 (Fig. S2); 85% of those who were not eligible for randomization were disqualified because of a below-threshold allergic response (according to the results of the skin-prick test, IgE level, food challenge, or all three) for one, two, or three foods. A total of 56% of the participants were boys, and the median age of all participants was 7.0 years (Table 1). Participants were highly atopic, with a median total IgE level of 700 IU per milliliter, and asthma, atopic dermatitis, allergic rhinitis, or all three were reported in a majority of the participants (Table S2). The median maximum tolerated doses of food protein in the challenges at baseline were similar for peanut and the six other foods (doses of 10 to 65 mg). The results were similar in the two groups with respect to all baseline measures except for the size of the response to peanut on skin-prick testing. The trial population is representative of patients with multiple food allergies except for a lower percentage of Hispanic participants than in the general population (Table S3). With regard to omalizumab dosing, 58% of participants received a median dose of 300 mg every 2 weeks, whereas the median dose was 225 mg in the 42% of participants who received omalizumab every 4 weeks. For individual participants, doses ranged from 75 mg every 4 weeks in 3 participants to 600 mg every 2 weeks in 5 participants.

EFFICACY

A total of 79 of the 118 participants who received omalizumab (67%) were able to consume a single dose of at least 600 mg of peanut protein without dose-limiting symptoms during the post-treatment challenge, as compared with 4 of the 59 participants who received placebo (7%) (between-group difference, 60 percentage points; 95% confidence interval [CI], 47 to 70; $P<0.001$) (Table 2 and Fig. 1). Except for cashew, there were similar between-group differences with respect to the prespecified key secondary end points (cashew, egg, and milk), as well as the other three foods.

Individual participant trajectories for peanut and the six other foods are shown in Figure S3. The median pre- and post-treatment challenge thresholds increased from baseline for all seven foods among the participants who received omalizumab but not among those who received placebo. The median post-treatment cumulative thresholds among the participants who received omalizumab were at least 4044 mg for all foods except cashew (median,

444 mg). The percentage of participants receiving omalizumab who could consume each incremental post-treatment challenge dose without dose-limiting symptoms was higher than the percentage among those receiving placebo (Fig. 2 and Table S6).

OTHER SECONDARY END POINTS

The percentage of participants who successfully consumed one, two, or three foods, overall and at each dose increment, was also assessed (Fig. 3 and Table S7). For consumption of any one food, 80% of participants receiving omalizumab consumed a cumulative dose of 1044 mg without adverse effects, 78% consumed 2044 mg, 75% consumed 4044 mg, and 66% consumed 6044 mg. These percentages fell to 69%, 66%, 54%, and 42%, respectively, for consumption of two foods and to 47%, 37%, 31%, and 24% for consumption of three foods.

We assessed the effects of a longer duration of treatment (40 to 44 weeks vs. 16 to 20 weeks) in the open-label extension involving the participants who had received omalizumab in the first stage of the trial (Fig. S4). Challenge thresholds for most participants either remained the same or increased (for peanut, thresholds in 45% of the participants were unchanged, thresholds in 34% were higher, and thresholds in 21% were lower). The median changes per food ranged from 0 to 2000 mg. Most decreases were small, although one participant had a decrease from 4044 mg to 444 mg in the cumulative dose of peanut that the participant could consume without adverse effects.

The quality of life of the participants and caregivers was also assessed, with the use of validated Food Allergy Quality of Life questionnaires.[22,23] No changes were seen in either the caregiver or participant scores at the end of the first stage of the trial as compared with the scores at baseline (Table S8). Changes were observed in the open-label extension, as described in the Supplementary Appendix.

SAFETY

The incidence and severity of adverse events and the subset of treatment-related adverse events were similar in the two groups (Tables S10A and S10B), with the exception of injection-site reactions, which were more common in the omalizumab group. One serious adverse event occurred in a 1-year-old participant in whom liver enzyme levels became elevated during the first stage of the trial (Table S9A); the participant was withdrawn from the trial and the child’s parents were informed of the child’s assigned group (omalizumab); the serious adverse event was determined to be possibly related to omalizumab, but a complete evaluation concluded that omalizumab was unlikely to be the cause. There were no serious adverse events reported in the open-label extension (Table S9B).

UNANTICIPATED ISSUES

The trial overlapped with the Covid-19 pandemic, which led to an interruption in recruitment and administration of omalizumab or placebo. A total of 42 participants who had undergone randomization had to stop and then restart the first stage of the trial or the open-label extension (all participants restarted). In addition, mold growth was identified in a small number of food products that were being used in oral food challenges, which resulted in a temporary halt of all challenges. Measures were undertaken to resolve this issue and

sensitivity analyses were performed to ensure that the trial results had not been affected; these analyses indicated that the trial outcomes were unaffected (see the Supplementary Appendix and Tables S11A and S11B).

DISCUSSION

In persons with multiple food allergies who were as young as 1 year of age, omalizumab treatment for 16 weeks was superior to placebo in increasing the reaction threshold for peanut, cashew, egg, and milk; 67% of the participants who received omalizumab were able to successfully consume at least 600 mg of peanut protein (cumulative dose, 1044 mg, equivalent to approximately 4 peanuts), and 44% were able to successfully consume a cumulative dose of 6044 mg (equivalent to approximately 25 peanuts, the highest dose used in the first stage of the trial).[24] This effect for peanut is consistent with that seen in previous studies,[11,25,26] and in this trial similar effects were seen for all the foods studied.

These levels of protection are likely to exceed those that would be needed for the amounts of food that are typically encountered during accidental exposure,[27] which highlights the possible use of omalizumab as monotherapy to reduce the daily risk of food allergic reactions while recognizing that this protection would require ongoing dosing as well as continued avoidance of allergenic foods.[24,28] Furthermore, omalizumab improved the ability to consume multiple foods without adverse effects; for example, 80% of the participants were able to consume a cumulative dose of 1044 mg of any one food without adverse effects, 69% were able to consume 1044 mg of two foods, and 47% were able to consume 1044 mg of three foods. This finding could be important for persons who have multiple food allergies, because this amount of food protein is larger than a whole nut, a bite of a baked good, or a sip of milk, and omalizumab could provide day-to-day protection irrespective of the specific food allergy. Additional treatment for 24 weeks in the open-label extension trial appeared to show the durability of this response, with most participants showing stable or increased challenge thresholds. No differences in quality of life were detected during the blinded phase of the trial.

This trial included participants as young as 1 year of age. The prevalence of food allergy peaks at 1 to 2 years of age, and although some of these allergies will be outgrown, many are severe and persistent, and the preschool-age years are a time of exceptionally high risk of accidental exposures.[29] Retention was high (97%), even with the interruption caused by the Covid-19 pandemic. The small percentage of participants who withdrew from our trial is in stark contrast to the 15 to 25% of participants who withdraw from most oral immunotherapy trials.[7,30]

We observed substantial variability in response and some clear treatment failures. Some of the failures may be explained by the specific criteria used to define success. For example, a participant whose maximum tolerated dose changed from 3 to 300 mg would have substantial protection against small, accidental exposures but would not have met the end-point criteria. However, 14% of participants could not consume 30 mg of peanut without dose-limiting symptoms, which most would consider a treatment failure.

The trial also has limitations. Only three adults were included, and the cohort was mostly non-Hispanic and White, which could reduce the generalizability of the results. Also, modified asthma-based dosing of omalizumab was used on the basis of doses in previous studies,[11,13–15,25] which excluded persons with high baseline IgE levels, many of whom might be excellent candidates for this therapy.

This phase 3 trial involving patients as young as 1 year of age with multiple food allergies showed that 16 weeks of treatment with omalizumab substantially increased threshold reactivity to peanut and multiple other foods to levels that could protect against allergic reactions associated with accidental exposure. Reactions to such exposures are common and often severe, leading to negative effects on quality of life and the need for constant vigilance. Additional studies will be needed to elucidate more fully the reasons for treatment failures, as well as the possibility that disease modification, as opposed to protection while receiving therapy, could be seen with early and prolonged use.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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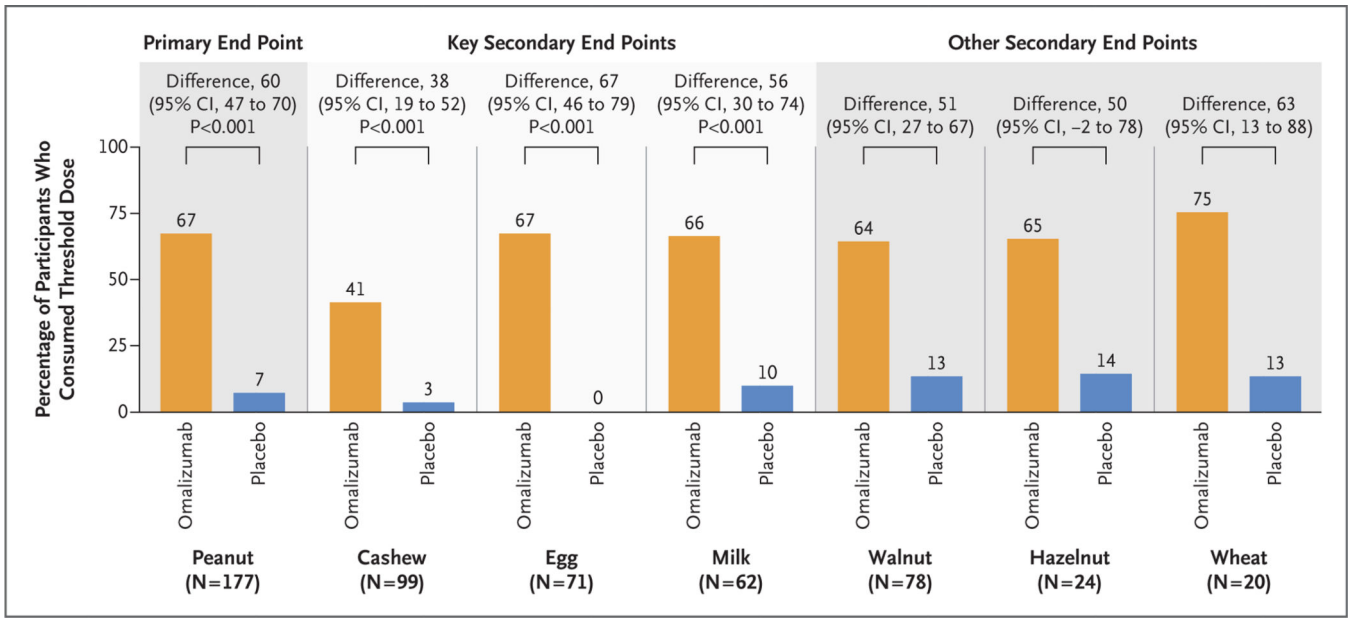

Figure 1. Successful Consumption of Prespecified Threshold Dose at Week 16.

Shown are the percentages of participants in the two groups who consumed the prespecified threshold doses without dose−limiting symptoms during food challenges at the end of the first stage of the trial; these food challenges were started at week 16 and were conducted during separate visits spanning up to a 4−week period. The prespecified threshold dose of peanut protein was a single dose of at least 600 mg; for cashew, egg, milk, walnut, hazelnut, and wheat protein, the prespecified threshold was a single dose of at least 1000 mg. The 95% confidence intervals for the differences were calculated with the use of exact unconditional confidence limits. The P values for the primary and key secondary end points are unadjusted, two−sided values derived from Fisher's exact test.

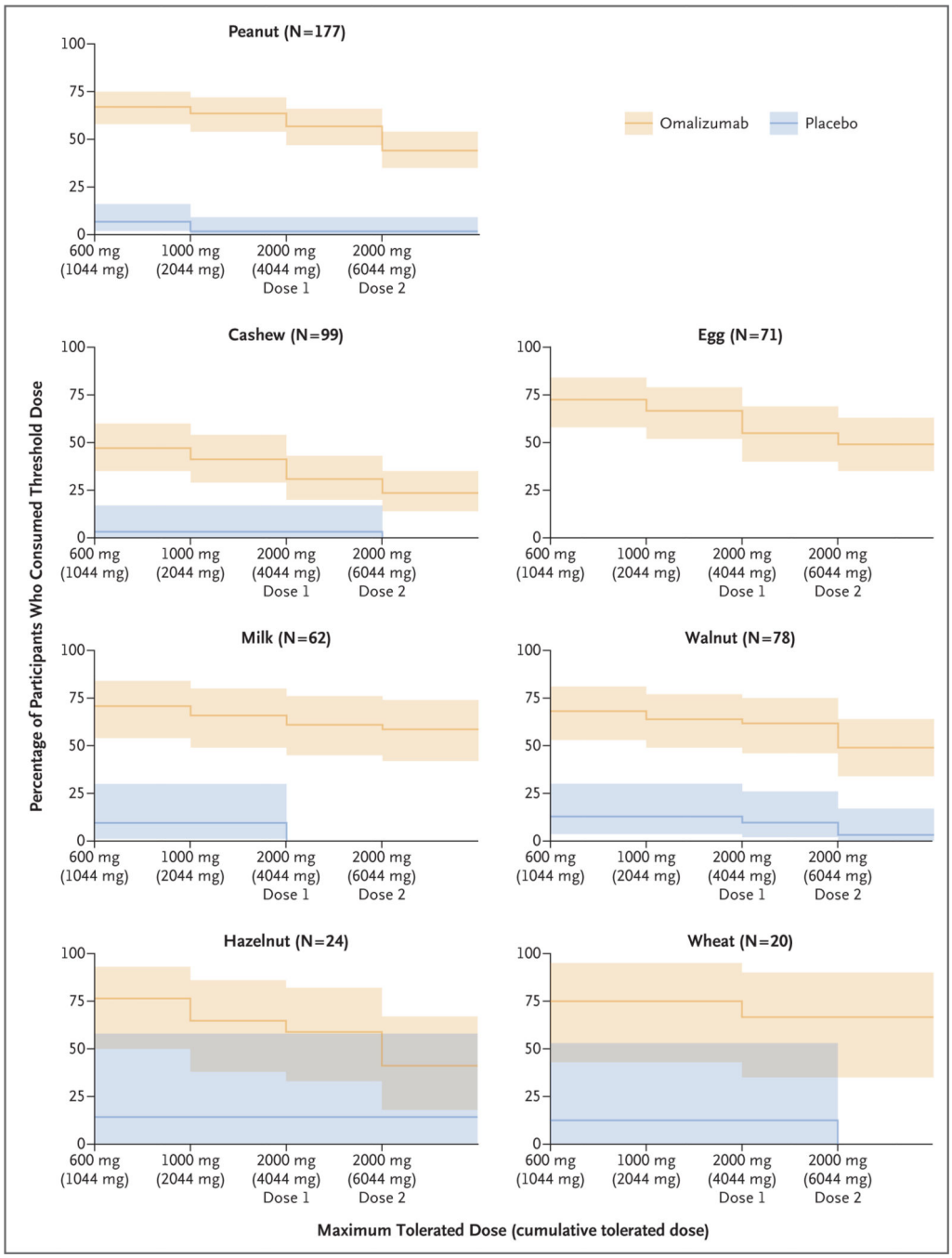

Figure 2. Successful Consumption of Prespecified Secondary End-Point Doses at Week 16.
Shown are the percentages of participants in the two groups who consumed the prespecified threshold doses and the cumulative doses without dose−limiting symptoms. The 95% confidence intervals for each group were calculated with the use of exact confidence limits, which are based on a score statistic. The food challenges at the end of the first stage of the trial were started at week 16 and were conducted during separate visits spanning up to a 4−week period.

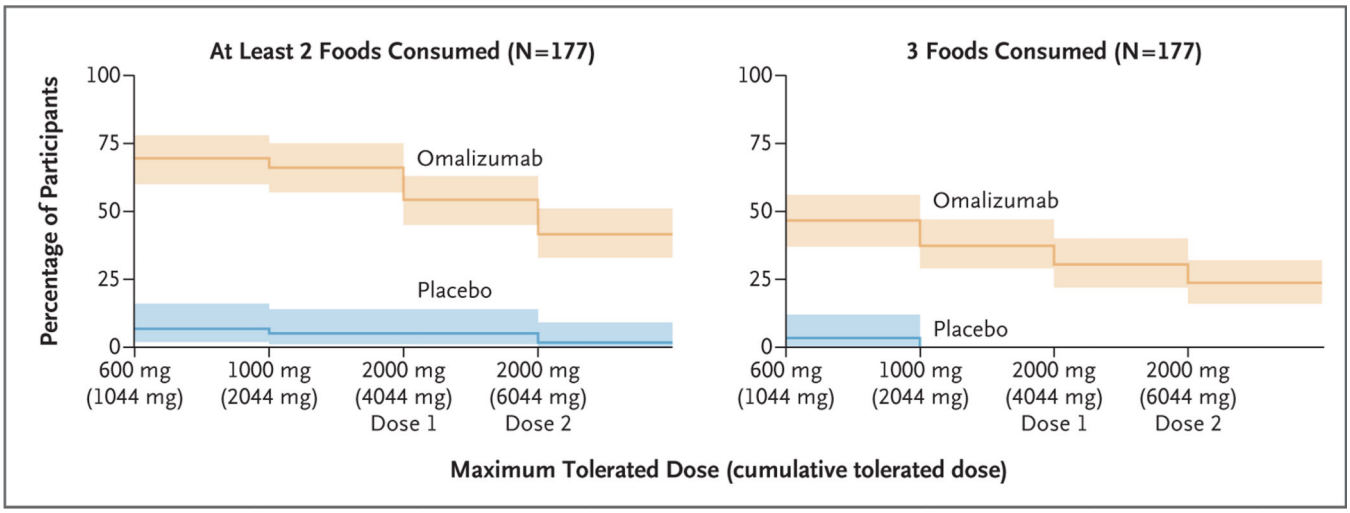

Figure 3. Successful Consumption of Multiple Foods at Prespecified Secondary End-Point Doses at Week 16.

Shown are the percentages of participants who consumed prespecified doses and cumulative doses of at least two foods and of all three foods without dose-limiting symptoms. The 95% confidence intervals for each group were calculated with the use of exact confidence limits, which are based on a score statistic. The food challenges at the end of the first stage of the trial were started at week 16 and were conducted during separate visits spanning up to a 4-week period.

Table 1.

Baseline Demographic Characteristics and Allergy Test Results of Participants.*

Variable	Omalizumab N = 118	Placebo N = 59
Male sex — no. (%)	69 (58%)	31 (53%)
Age — yr	6.5 (4.0–11.0)	7.0 (3.5–11.0)
Median total IgE level (IQR) — IU/ml	700 (441–954)	712 (446–1035)
Allergy to peanut — no. of participants	118	59
Median skin-prick test (IQR) — mm†	13.5 (9.0–18.5)	16.0 (10.8–20.5)
Median allergen-specific IgE level (IQR) — kUA/liter‡	72 (23–170)	88 (27–198)
Median maximum tolerated dose (IQR) — mg	30 (10–30)	30 (10–30)
Allergy to cashew — no. of participants	68	31
Median skin-prick test (IQR) — mm	15.0 (10.5–20.0)	16.0 (10.0–22.5)
Median allergen-specific IgE level (IQR) — kUA/liter	31 (16–72)	31 (11–55)
Median maximum tolerated dose (IQR) — mg	10 (3–10)	3 (2–30)
Allergy to egg — no. of participants	51	20
Median skin-prick test (IQR) — mm	12.5 (9.0–18.0)	14.3 (10.0–16.1)
Median allergen-specific IgE level (IQR) — kUA/liter	28 (16–54)	38 (22–97)
Median maximum tolerated dose (IQR) — mg	10 (10–30)	10 (3–30)
Allergy to milk — no. of participants	41	21
Median skin-prick test (IQR) — mm	14.5 (11.0–16.5)	16.5 (10.5–18.0)
Median allergen-specific IgE level (IQR) — kUA/liter	37 (25–93)	32 (15–61)
Median maximum tolerated dose (IQR) — mg	30 (10–100)	10 (10–30)
Allergy to walnut — no. of participants	47	31
Median skin-prick test (IQR) — mm	14.0 (9.5–17.0)	11.5 (7.0–15.5)
Median allergen-specific IgE level (IQR) — kUA/liter	24 (11–63)	25 (9–39)
Median maximum tolerated dose (IQR) — mg	30 (10–100)	30 (10–100)
Allergy to hazelnut — no. of participants	17	7
Median skin-prick test (IQR) — mm	12.0 (9.5–19.5)	4.5 (4.3–9.5)
Median allergen-specific IgE level (IQR) — kUA/liter	18 (10–57)	12 (7–18)
Median maximum tolerated dose (IQR) — mg	3 (3–10)	30 (6–65)
Allergy to wheat — no. of participants	12	8

Variable	Omalizumab N = 118	Placebo N = 59
Median skin−prick test (IQR) — mm	9.3 (8.4–13.0)	11.3 (10.0–13.0)
Median allergen−specific IgE level (IQR) — kUA/liter	38 (22–96)	38 (20–79)
Median maximum tolerated dose (IQR) — mg	100 (25–100)	20 (8–100)

[*] IQR denotes interquartile range.

[†] Skin−prick testing was performed with the use of the Greer Pick device and extracts (Stallergenes Greer, Lenoir, NC). A positive result is defined as a skin−prick test result that is greater than 3 mm.

[‡] Allergen−specific IgE levels were measured by means of ImmunoCAP (Thermo Fisher Scientific, Waltham, MA). A positive result is defined as an allergen−specific IgE level higher than 0.35 kUA per liter.

Table 2.

Successful Consumption of Prespecified Threshold Dose at Week 16.*

End Point and Food Challenge	No. of Participants	Omalizumab	Placebo	Difference (95% CI)	P Value
		no./total no. (%)		*percentage points*	
Primary end point†					
Peanut	177	79/118 (67)	4/59 (7)	60 (47 to 70)	<0.001
Key secondary end points‡					
Cashew	99	28/68 (41)	1/31 (3)	38 (19 to 52)	<0.001
Egg	71	34/51 (67)	0/20 (0)	67 (46 to 79)	<0.001
Milk	62	27/41 (66)	2/21 (10)	56 (30 to 74)	<0.001
Other secondary end points‡					
Walnut	78	30/47 (64)	4/31 (13)	51 (27 to 68)	—
Hazelnut	24	11/17 (65)	1/7 (14)	50 (−2 to 78)	—
Wheat	20	9/12 (75)	1/8 (13)	63 (13 to 88)	—

* The food challenges at the end of the first stage of the trial were started at week 16 and were conducted during separate visits spanning up to a 4−week period. The 95% confidence intervals (CIs) are exact unconditional confidence intervals. P<0.001 (unadjusted two−sided P value from Fisher's exact test) for the primary end point and the key secondary end points.

† The primary end point was consumption of a single dose of at least 600 mg of peanut protein, without dose−limiting symptoms. This end point was tested at the P<0.0001 level of significance at the interim analysis, which included 165 children and adolescents.

‡ The secondary end points were consumption of a single dose of at least 1000 mg of food protein without dose−limiting symptoms. Key secondary end points, which were tested only if the primary end point was significant at P<0.0001 at the interim analysis, were tested at the P<0.005 level of significance. The other secondary end points were not included in the plan to adjust for multiple testing results and are reported with 95% confidence intervals, without P values; the 95% confidence intervals are not adjusted for multiple testing and should not be used to infer treatment effects.