Exploratory analyses of predictors and correlates of response to omalizumab therapy in patients with multiple food allergies

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Background: Stage 1 of the Omalizumab as Monotherapy and as Adjunct Therapy to Multi-Allergen OIT in Food Allergic Children and Adults (OUtMATCH) study demonstrated that treatment with omalizumab for 16 to 20 weeks significantly increased the reaction threshold for peanut and other common food allergens in participants with multiple food allergies. However, the degree of this protection is variable across participants, and there are no known markers to predict or assess individual response to omalizumab.

Objective: Our aim was to evaluate clinical and laboratory-based variables as predictors or correlates of response to omalizumab treatment.

Methods: Cumulative tolerated dose (CTD) as a continuous variable and thresholds of 444 mg and 1044 mg of individual food proteins were selected as definitions of positive treatment response. Clinical and immunologic variables were evaluated as predictors of response.

Results: Omalizumab treatment reduced the level of free IgE. In this exploratory analysis (N = 116), although not definitive, higher total IgE level at baseline was the most consistent predictor of a positive response to omalizumab treatment (peanut CTD: $r = 0.25$; $q = 0.047$). Omalizumab dosing frequency (every 2 weeks) was also associated with higher peanut CTD outcomes ($r = 0.25$; $q = 0.047$). Medical history of allergy, level of allergen-specific IgE, skin prick test result, and basophil activation did not consistently correlate with response to omalizumab treatment. Concomitant peanut and milk allergy was positively correlated with outcomes of omalizumab treatment ($r = 0.34$; $q = 0.003$), whereas peanut allergy concomitant with either cashew allergy ($r = -0.43$; $q = 0.003$) or walnut allergy ($r = –0.26$; $q = 0.042$) was inversely correlated with outcomes of omalizumab treatment.

Conclusion: Of the food allergy biomarkers and omalizumab dosing assessed in this analysis, a higher baseline total IgE level was the most consistent, albeit modest, predictor of successful peanut threshold protection with omalizumab treatment, thus warranting further study. (J Allergy Clin Immunol 2026;157:442-53.)

Key words: *Predictors, correlates, basophil activation, food challenges, omalizumab, food allergy, IgE, anti-IgE*

Stage 1 of the Omalizumab as Monotherapy and as Adjunct Therapy to Multi-Allergen OIT in Food Allergic Children and Adults (OUtMATCH) double-bind randomized controlled trial demonstrated that 16 to 20 weeks of treatment with the anti-IgE antibody omalizumab significantly increases the amount of food protein tolerated during double-blind, placebo-controlled food challenges (DBPCFCs) in those with IgE-mediated food allergy.[1] This effect was shown for peanut and other studied foods, including cashew, egg, hazelnut, milk, walnut, and wheat. These findings led to US Food and Drug Administration approval of omalizumab for the reduction of allergic reactions resulting from accidental exposure in patients aged 1 year and older with

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Abbreviations used
BAT: Basophil activation test
CTD: Cumulative tolerated dose
DBPCFC: Double-blind placebo-controlled food challenge
FDR: False discovery rate
NPV: Negative predictive value
OUtMATCH: Omalizumab as Monotherapy and as Adjunct Therapy to Multi-Allergen OIT in Food Allergic Children and Adults
sIgE: Specific IgE
SPT: Skin prick test
tIgE: Total IgE

IgE-mediatedallergies to 1 or more foods.[2] Although this repre
sentsa significant step forward for those burdened by food allergy, response to treatment was variable among omalizumab-treated participants. Within the omalizumab treatment group, 24% of participantstolerated the maximum dose of all 3 target foods (a cumulativetolerated dose [CTD] of 6044 mg) following treatment,whereas 14% of participants were unable to tolerate beyond acumulative amount of peanut protein of 44 mg.

Therefore,although omalizumab provides a therapeutic option forsingle or multiple food allergies and provides protection against accidental ingestion for most patients, the range of treatment responsespresents challenges in identifying optimal candidates for therapy and predicting the level of protection afforded by omalizumab. Although oral food challenges remain the standard formeasuring treatment response, they are resource-intensive, are time-consuming,carry risks, and can cause anxiety. Identification ofboth baseline predictors of success and markers of therapeutic response would be ideal. In this report, we investigate baseline factors and longitudinal biologic markers that may predict a clinicallymeaningful response to omalizumab.[3,4]

METHODS

Study participantss The full study protocol and statistical analysis plan for the OUtMATCH study can be found in the supplement to the stage 1 primarypublication.[1] Participants who completed stage 1 of the OUtMATCH study were included in these analyses (for addi
tionaldetails, see the Supplementary Methods in the Online Repository at www.jacionline.org). Predictors and correlates of response following active omalizumab treatment were studied forpeanut (n = 116) and other target foods (cashew [n = 67], egg [n =51], milk [n = 39], and walnut [n = 45]); the sample sizesfor hazelnut (n = 17) and wheat (n = 12) were insufficient forthese analyses. Correlates of immune markers were also evaluatedfor participants treated with omalizumab (n = 116) and participantswho received placebo (n = 60, Fig E1). In accordance withthe OUtMATCH design, for participants with allergy to 3 ormore foods other than peanut, only 2 of the coallergens were chosenand assessed throughout the study (based on shared decisionmaking with participants and/or parents or legal guardians [seethe Supplementary Methods]) and are referred to as target foods. The absence of a food among a participant's studyspecific target foods is not necessarily an indication that the participantdid not have allergy to that food. The most common combinationsof allergens studied in the omalizumab arm were peanut, cashew, and walnut (n = 31), followed by peanut, egg, and milk (n=22 [see Table E1 in the Online Repository at www.jacionline.org]).

Statistical analyses and interpretation plan

This is an exploratory analysis that is intended to be hypothesis-generating with the goal of identifying promising predictors and correlates of therapeutic response to omalizumab. Analyses were not prespecified. Associated *P* values are presented alongside *q* values from an adjustment of false discovery rate (FDR), which adjusts for multiple tests by also considering the expected number of false-positive results among all rejected null hypotheses. This adjustment is made within each predictor target food end point (eg, peanut CTD, a peanut CTD of ≤444 mg) and within each correlational target food CTD analysis separately. We discuss both unadjusted *P* values and FDR *q* values, which account for multiplicity to broadly identify potential predictors that warrant further study. To this end, analyses with unadjusted *P* values less than .05 are considered indicative of promising predictors; those that also have an FDR *q* value less than 0.05 show stronger potential.

Analyses were performed for single and multiple allergens using univariate and decision tree approaches. Only one-third of the stage 1 trial participants were in the placebo arm, and very few of them had successful outcomes. Because effects within the omalizumab group are of primary interest and because there is insufficient power to assess interactions of treatment group within analyses having so few successes for placebo, most analyses were limited to variation of outcome within the omalizumab treatment group.

A modified asthma-based dosing of omalizumab was utilized for this study.[5-7] CTD for single allergens was evaluated by using 3 distinct outcomes: (1) CTD treated as a continuous variable; (2) CTD success or failure, with success defined as achieving tolerance of at least 444 mg of protein at the end of the stage 1 DBPCFCs, and (3) CTD success or failure, with success defined as achieving tolerance of at least 1044 mg of protein at the end of the stage 1 DBPCFCs. The thresholds of 444 mg and 1044 mg of cumulative protein were chosen as relevant for accidental exposures,[3,8-10] and they were also evaluated for multiple allergens. These thresholds are less stringent than the previously published OUtMATCH primary outcome for peanut (1044 mg) and target foods (2044 mg).[1]

The inputs for multivariate analyses using decision trees included 12 baseline variables that were chosen because they can be readily available to a clinician: (1) demographic parameters (weight, body mass index, age, sex, and presence vs absence of other atopic disease [atopic dermatitis, allergic rhinitis, asthma]), (2) immune parameters (total IgE [tIgE] level, specific IgE [sIgE] level skin prick test [SPT] results, and ratio of sIgE to tIgE [single food analyses only]), (3) omalizumab dosing frequency (every 2 weeks vs every 4 weeks), and (4) omalizumab dose. The basophil activation test (BAT) was not included owing to limited clinical availability. Decision tree statistics identify parameter cut points that differentiate the likelihood of success. As discussed later, specifically for IgE, positive predictive values are the proportion of successes among all participants with a value above the cut point, whereas negative predictive values (NPVs) are the proportion of failures among those participants below the cut point. For details about specific statistical procedures, see the Supplementary Methods.

RESULTS

Predictors of single-allergen food challenge outcomes: CTD

Peanut-specific findings. In univariate analyses of peanut CTD as a continuous variable, omalizumab-treated participants with a higher baseline tIgE level ($r = 0.25$; $P = .008$; $q = 0.047$) had higher peanut CTDs at the end of stage 1 (Table I). Higher peanut CTDs were also associated with the 2-week dosing frequency ($r = –0.25$; $P = .008$; $q = 0.047$). When peanut CTD was evaluated as a continuous variable by tIgE level quintile, the median peanut CTD was lower in the first quintile (tIgE level range = 140-383 IU/mL; median CTD = 744 mg) than in the next 4 tIgE level quintiles (tIgE level range = 383-3100 IU/mL: median CTD range = 4044-6044 mg [Fig 1, *A*]). This relationship between higher tIgE level and peanut CTD can be further visualized in Fig 1, *B*, which also shows omalizumab dosing frequency.

Only a few additional predictors of peanut response were detected. Inclusion of specific target foods appeared to be related to responses to peanut treatment: milk as a target food allergen was associated with higher peanut CTD (milk $r = 0.34$; $P = .001$; $q = 0.003$ [Table I]), whereas cashew ($r = –0.34$; $P < .001$; $q = 0.003$) and walnut ($r = –0.26$; $P = .004$; $q = 0.042$) were associated with poorer responses. No significant associations with baseline basophil activation test (BAT) parameters were found. The BAT stimulation of 10 μg/mL of peanut suggested a positive relationship with peanut CTD based on the unadjusted P value ($r = 0.25$; $P = .012$; $q = 0.060$), but the relationship was not significant after adjustment for the FDR.

Treatment response for other target food allergens. For cashew, there was also a positive correlation between cashew CTD and higher tIgE level based on the unadjusted P value ($r = 0.28$; $P = .020$; $q = 0.19$ [see Table E2 in the Online Repository at www.jacionline.org]). Similarly, higher cashew CTD correlated with 2-week omalizumab dosing frequency ($r = –0.25$; $P = .040$; $q = 0.23$). There were no correlations with the cashew sIgE/tIgE ratio or cashew BAT parameters with cashew CTD. Additional associations between cashew CTD and the inclusion of specific target foods were observed, with a positive correlation between the inclusion of milk as a target food and higher cashew CTD ($r = 0.32$; $P = .007$; q = 0.11) and a negative correlation with walnut as a target food ($r = –0.32$; $P = .008$; $q = 0.11$). However, none of these effects were significant after FDR adjustment.

For egg, milk, or walnut CTDs assessed as continuous outcome measures, no correlations with baseline variables were identified (see Table E2).

Additionally, there was no correlation between days from last omalizumab injection and CTD (data not shown).

Predictors of omalizumab response to a CTD of 444 mg of protein

We also sought to identify predictors of specific thresholds of particular clinical relevance. A CTD of 444 mg or higher was identified as a clinically relevant threshold that might be encountered with an accidental exposure.[3,4] Overall 70% of participants achieved a CTD of at least 444 mg for all 3 of their target foods (see Fig E2, *A* available in the Online Repository at www.jacionline.org).

A total of 89 participants (77% [89 of 116]) achieved a peanut CTD of at least 444 mg. A higher peanut CTD was associated with a higher tIgE level ($P = .022$; $q = 0.33$) and an omalizumab dosing frequency of 2 weeks based on the unadjusted P value ($P = .031$; $q = 0.33$) (Table II). Cashew as a target food was associated with failure of peanut at the 444-mg threshold by the same criterion ($P = .006$; $q = 0.15$ [Table II and see Figs E3 and E4 in the Online Repository at www.jacionline.org]). Notably, 90% of participants who did not have cashew as a target food (43 of 48) successfully consumed 444 mg of peanut protein compared with 68% of participants who included cashew as a target allergen (46 of 68); however, these results were not significant after FDR adjustment.

For the 444-mg threshold, the rate of success among the other allergens varied: 66% (44 of 67 participants) for cashew, 84% (43 of 51 participants) for egg, 87% (34 of 39 participants) for milk, and 71% (32 of 45 participants [Fig 2, *A*]) for walnut, but no predictors were found for CTD thresholds of 444 mg (Fig 2, *A* and see Tables E3-E6 [in the Online Repository at www.jacionline.org], respectively, per allergen and Fig E3).

Predictors of omalizumab response to a CTD of 1044 mg of protein

Overall, 57% of participants achieved a CTD of 1044 mg or higher for all 3 of their target foods (Fig E2, *B*) and 71% of participants were successful at the 1044-mg CTD threshold for peanut (82 of 116 [Table III and Fig 2, *B*). Success was associated with higher baseline tIgE level ($P = .003$; $q = 0.051$) and 2-week dosing frequency ($P = .004$; $q = 0.051$) based on the unadjusted P value, but the relationship was not significant after FDR adjustment. A higher baseline BAT response to stimulation with10 ug/mL of peanut had an association with success based on the unadjusted P value ($P = .025$; $q = 0.12$), but the association was not significant after FDR adjustment (Table II).

Participants who included cashew as a target food were less likely to achieve the 1044-mg peanut threshold (62%) than were participants who did not include cashew as a target food (83% [$P = .012$; $q = 0.10$ [Table III and see Figs E5 and E6 (in the Online Repository at www.jacionline.org)]). Conversely, participants who included milk as a target food had greater success in achieving a CTD of 1044 mg for peanut (85%) than did those who did not include milk as a target food (64% [$P = .019$; $q = 0.12$]). These results were based on unadjusted P values, but they did not persist after FDR correction.

For cashew, 49% of participants successfully tolerated the 1044-mg CTD (33 of 67) (Fig 2, *B* and see Table E7 [in the Online Repository at www.jacionline.org]). For other target foods, success at the 1044-mg CTD level was similar (Fig 2, *B* and see Tables E8 and E10 [in the Online Repository at www.jacionline.org]). Only milk showed some variables associated with the 1044-mg CTD, but none was significant after FDR correction (see Table E9 in the Online Repository at www.jacionline.org).

Predictors of omalizumab response to single or multiple foods

We next aimed to identify which baseline variables were most predictive of success when considering the influence of other variables. Specifically, we explored the relative significance of tIgE level and dosing regimen, as they are inherently linked. To this end, decision tree modeling was completed for peanut and the

TABLE I. Baseline predictors of peanut CTD during the oral food challenge at the end of stage 1 (participants who received omalizumab)

Characteristic	Sample size	Descriptive statistics	Spearman rank correlation		
			Correlation	*P* value	*q* value*
Age (y), median (IQR)	116	8.0 (4.0-11.0)	–0.09	.36	0.51
Pooled age group (y), no. (%)	116		–0.10	.31	0.51
≤ 5		43 (37%)			
6-11		45 (39%)			
≥ 12		28 (24%)			
Sex (male), no. (%)	116	68 (59%)	–0.06	.53	0.64
Dose frequency. no. (%)†	116		–0.25	**.008**	**0.047**
Every 2 wk		68 (59%)			
Every 4 wk		48 (41%)			
Height (cm), median (IQR)	116	125 (105-149)	–0.13	.17	0.50
Weight (kg), median (IQR)	116	26 (18-41)	–0.13	.16	0.50
Body mass index, median (IQR)	116	16.85 (15.59-18.65)	–0.06	.53	0.64
Medical history, no. (%)					
Allergic rhinitis	116	69 (59%)	0.09	.34	0.51
Atopic dermatitis	116	93 (80%)	0.02	.80	0.89
Asthma	116	58 (50%)	0.10	.28	0.51
Target food, no. (%)	116				
Cashew		68 (59%)	–0.34	**<.001**	**0.003**
Egg		51 (44%)	0.21	**.022**	0.095
Milk		39 (34%)	0.34	**<.001**	**0.003**
Walnut		45 (39%)	–0.26	**.004**	**0.042**
Hazelnut		18 (16%)	0.00	.96	0.96
Wheat		11 (9.5%)	0.10	.30	0.51
CTD (mg of protein), no. (%)	116		0.07	.45	0.58
0		2 (1.7%)			
1		3 (2.6%)			
4		18 (16%)			
14		24 (21%)			
44		69 (59%)			
Peanut SPT result (mm), median (IQR)‡	116	13.5 (8.8-18.5)	–0.10	.30	0.51
Peanut sIgE level (kUA/L), median (IQR)	116	70 (23-172)	0.02	.87	0.93
tIgE level (IU/mL), median (IQR)	116	736 (410-1058)	0.25	**.008**	**0.047**
Peanut sIgE/tIgE, median (IQR)	116	0.11 (0.04-0.24)	–0.18	.050	0.19
BAT result, median (IQR)					
Unstimulated basophils	100	2.2 (1.2-4.2)	0.08	.41	0.55
fMLP level (1 μM)	99	34 (19-52)	0.10	.31	0.51
Anti-IgE level (1 μg/mL)	99	15 (5-41)	0.11	.26	0.51
0.001 μg/mL	100	10 (3-25)	–0.01	.91	0.95
0.01 μg/mL	100	18 (5-47)	0.03	.75	0.87
0.1 μg/mL	99	21 (6-51)	0.10	.30	0.51
1 μg/mL	99	14 (5-36)	0.12	.23	0.51
10 μg/mL	100	24 (11-60)	0.25	**.012**	0.060
Area under the curve	98	63 (30-165)	0.10	.33	0.51

Bolding denotes *P* value less than .05 or *q* value less than 0.05.
fMLP, *N*-formylmethionyl-leucyl-phenylalanine; *IQR*, interquartile range.
*FDR correction for multiple testing.
†Every 2 weeks is the reference value (ie, the lower value for purposes of interpreting the correlation). Participants with less frequent dosing (every 4 weeks) tended to have a lower CTD than those with more frequent dosing (every 2 weeks).
‡SPT was performed with use of the Greer Pick device and extracts (Stallergenes Greer, Lenoir, NC). A positive result is defined as an SPT result that is at least 4 mm greater than the negative control.

other allergens for the 444-mg and 1044-mg thresholds, as well as for 1, 2, and 3 foods at each of these thresholds. Clinical variables identified from the univariate analyses (ie, tIgE level and dosing frequency) as well as from demographic and immune parameters and omalizumab dose when they were included in the tree models. Target foods were not included in this model. Across all 20 tree analyses conducted, either (1) tIgE level at baseline was identified as the primary variable for distinguishing between successes and failures in the omalizumab arm or (2) no variable was identified as useful. After pruning, tIgE level was the only variable identified for all trees summarized in Table IV, with the exception of cashew at 1044 mg as the dependent variable (inclusion of baseline sIgE level improved model fit [data not shown]) and all 3 foods at 1044 mg as the dependent variable (inclusion of baseline body mass index improved model fit [data not shown]). Total IgE levels exceeding the cut points identified in the decision tree analyses accurately identified outcome thresholds in 49.4% to 79.5% of cases (positive predictive value; leave-1-out cross-validation)

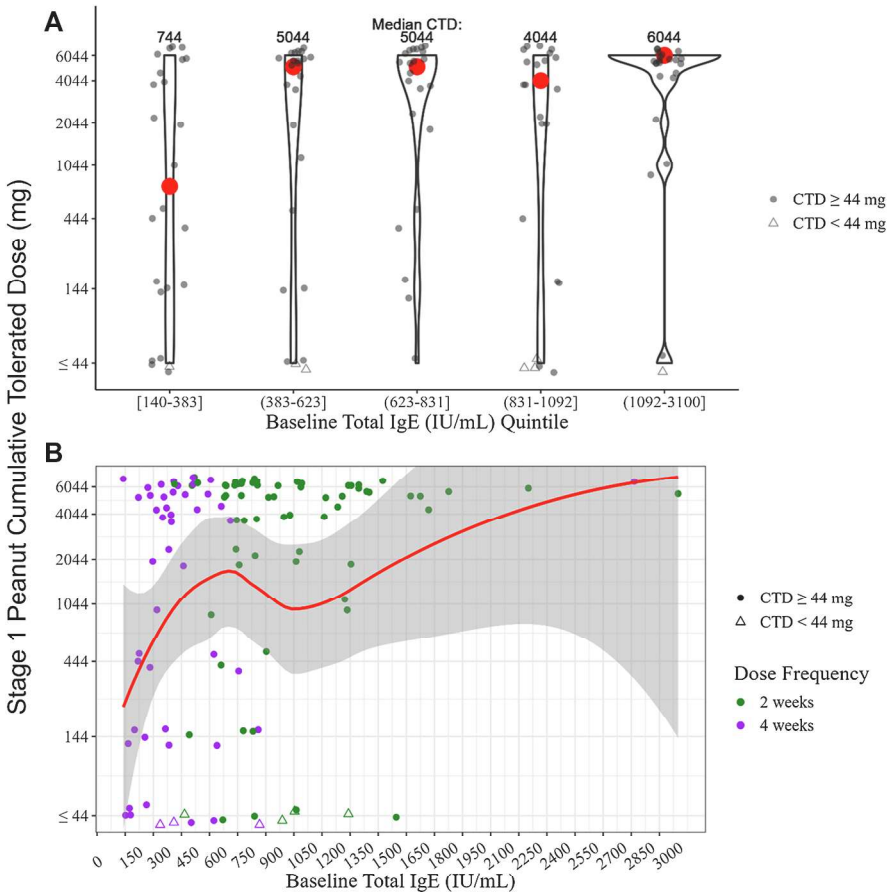

FIG 1. A, Distribution of end of stage 1 peanut CTD (mg) within baseline total IgE quintiles (omalizumab participants). Spearman-rank correlation between the 2 variables (P <.007). Median values are represented by red diamonds. **B,** Distribution of end of stage 1 peanut CTD (mg) within baseline total IgE level, including the locally estimated scatterplot smoothing (LOESS) curve (participants receiving omalizumab). Participants receiving omalizumab every 2 weeks (*green dots*) versus every 4 weeks (*purple dots*) are shown. Whereas the IgE level enrollment criteria (≤1850 IU/mL) and the participants' dosing were based on data collected early in the screening process and analyzed at local laboratories, the values used in the analyses were collected closer to the first dose of study drug and analyzed by a central laboratory. As a result, the values found for several participants extended above the enrollment criterion (≤3000 IU/mL) and/or outside of the parameters of the dosing table. Values below the 44-mg CTD were set at 44 mg for visualization purposes and are denoted by triangles. Values at or above the 44-mg CTD are denoted by circles. Plotting points are jittered horizontally and vertically.

and the NPV of the tIgE cut points ranged from 47.1% to 64.3%, with wide CIs. Bootstrapping was used to assess the sensitivity of tree results to the current population; the tIgE level findings were consistent with the results of analyses based on the original data.

Because tIgE level was the most consistent predictor for peanut and some other individual target foods, we evaluated the ability of tIgE level to predict the number of foods that were successfully consumed during the end of the stage 1 challenges at the 444-mg and 1044-mg thresholds (Fig 3). Overall, the 2 patterns looked similar in that there was a noticeable increase in median tIgE level for success with 1, 2, and 3 foods compared with success with 0 foods, although the differences were significant only at the 1044-mg threshold (P = .022). The median tIgE level was higher for the 3-foods success rate than for the 0-foods success rate for the 1044-mg outcome measure (Fig 3, *B*; for the 0 vs 3 success comparison, P = .0086).

Omalizumab-induced changes in biomarkers and their relationship to successful treatment

Compared with participants receiving place, participants receiving omalizumab were found to have smaller SPT wheal sizes(P <.001; q < 0.001), greater reductions in SPT wheal size (P = .15; q = 0.019), lower levels of free IgE (P <.001; q < 0.001),and reduced basophil activation at the end of stage 1 (P <.001; q < 0.001 [see Table E11 in the Online Repository at www.jacionline.org], Table V). However, these biomarker changeswere not shown to correlate with changes in oral food challengeoutcomes.

Omalizumabtreatment resulted in suppression of free IgE (IgE notbound by omalizumab) across all treated participants at the endof Stage 1 (see Table E11). However, no significant associations between BAT result or SPT result and food challenge outcomeswere found after correction for FDR (see Tables E12-

TABLE II. Baseline predictors of successful consumption of at least 444 mg of peanut protein during the oral food challenge at the end of stage 1 (participants who received omalizumab)

Characteristic	Sample size	Failure (n = 27)	Success (n = 89)	*P* value*	*q* value†
Age (y), median (IQR)	116	9.0 (4.0-12.0)	7.0 (4.0-10.0)	.45	0.69
Pooled age group (y), no. (%)	116			.37	0.66
≤ 5		10 (23%)	33 (77%)		
6-11		8 (18%)	37 (82%)		
≥12		9 (32%)	19 (68%)		
Sex (male), no. (%)	116			.33	0.66
Female		9 (19%)	39 (81%)		
Male		18 (26%)	50 (74%)		
Dosing frequency, no. (%)	116			**.031**	0.26
Every 2 wk		11 (16%)	57 (84%)		
Every 4 wk		16 (33%)	32 (67%)		
Height (cm), median (IQR)	116	139 (107-154)	124 (103-144)	.35	0.66
Weight (kg), median (IQR)	116	31 (18-48)	24 (17-37)	.17	0.54
Body mass index, median (IQR)	116	17.20 (15.75-19.80)	16.72 (15.54-18.48)	.16	0.54
Target food, no. (%)					
Cashew	116	22 (32%)	46 (68%)	**.006**	0.15
Egg	116	9 (18%)	42 (82%)	.20	0.57
Milk	116	6 (15%)	33 (85%)	.15	0.54
Walnut	116	13 (29%)	32 (71%)	.25	0.64
CTD (mg of protein), no. (%)	116			.73	0.93
0		0 (0%)	2 (100%)		
1		1 (33%)	2 (67%)		
4		5 (28%)	13 (72%)		
14		7 (29%)	17 (71%)		
44		14 (20%)	55 (80%)		
Allergen-specific SPT result (mm), median (IQR)‡	116	13.5 (8.5-23.0)	13.5 (9.0-18.0)	.53	0.73
Allergen sIgE level (kUA/L), median (IQR)§	116	69 (22-170)	72 (24-181)	.83	0.94
tIgE level (IU/mL), median (IQR)	116	503 (264-860)	752 (470-1087)	**.022**	0.26
Ratio of sIgE to tIgE, median (IQR)	116	0.17 (0.05-0.33)	0.11 (0.04-0.21)	.10	0.51
BAT result, median (IQR)					
Unstimulated basophils	100	2.2 (1.2-4.8)	2.2 (1.2-4.0)	.97	0.97
fMLP level (1 M)	99	37 (20-50)	32 (18-52)	.87	0.95
Anti-IgE level (1 g/mL)	99	19 (5-38)	13 (5-42)	.81	0.94
0.001 g/mL	100	8 (3-20)	11 (3-27)	.97	0.97
0.01 g/mL	100	16 (7-35)	18 (4-51)	.75	0.93
0.1 g/mL	99	16 (7-27)	22 (5-55)	.34	0.66
1 g/mL	99	13 (6-19)	15 (4-42)	.47	0.69
10 g/mL	100	16 (11-29)	28 (13-62)	.076	0.48
Area under the curve	98	58 (30-102)	75 (25-183)	.43	0.69

Bolding denotes *P* value less than .05 or *q* value less than 0.05.
fMLP, *N*-formylmethionyl-leucyl-phenylalanine; *IQR*, interquartile range.
*Wilcoxon rank sum test; Pearson chi-square test; Fisher exact test.
†FDR correction for multiple testing.
‡SPT was performed with use of the Greer Pick device and extracts (Stallergenes Greer, Lenoir, NC). A positive result is defined as an SPT result greater than 3 mm.
§Allergen-specific IgE levels were measured by using ImmunoCAP (Thermo Fisher Scientific, Waltham, Mass). A positive result is defined as an allergen-specific IgE level higher than 0.35 kUA/L.

E17 in the Online Repository at www.jacionline.org). tIgE and sIgE levels were not measured at the end of the stage 1 time point because of assay interference by omalizumab.

DISCUSSION

In February 2024, omalizumab was granted US Food and Drug Administration approval for the treatment of IgE-mediated food allergy in adults and pediatric patients aged 1 year and older. Although this approval represents a great step forward for food allergy therapy, a number of questions regarding the implementation of this therapy have emerged. As previously reported,[1] the degree of protection conferred by omalizumab appears variable across patients. Additionally, oral food challenges remain the standard in diagnosing food allergy and monitoring posttreatment response to omalizumab, highlighting the need for better predictive markers that are more easily attained. To identify biomarkers that could be relevant for real-world accidental exposures, we investigated the relationships of several measurements conducted in the OUtMATCH study by using various definitions of success when assessing response to omalizumab, including CTD as a continuous variable, as well as CTDs

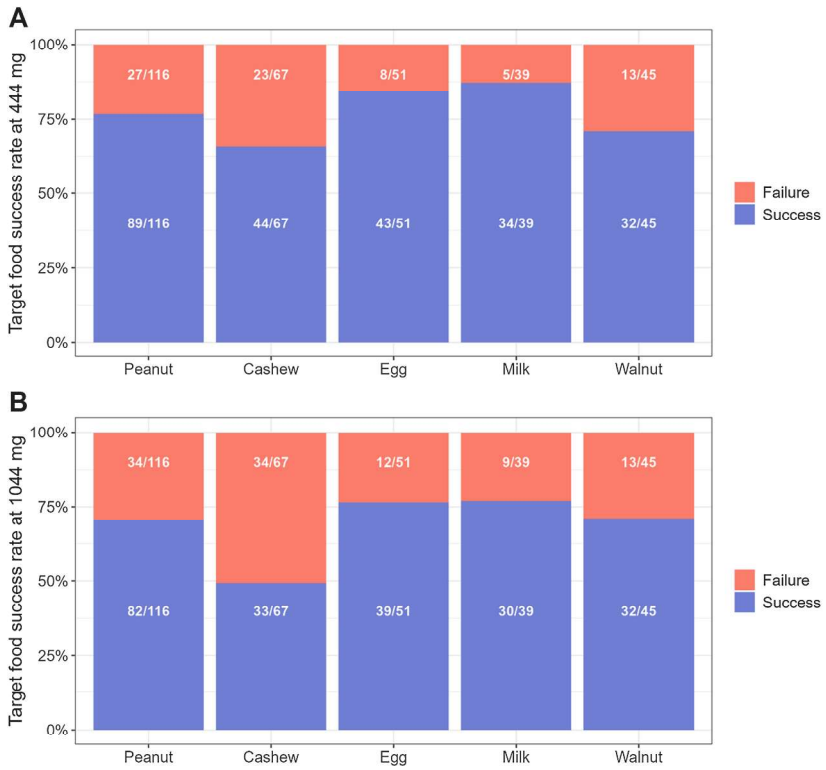

FIG 2. Target food success rates at clinically meaningful target food protein thresholds of at least 444 mg **(A)** and at least 1044 mg **(B)** during oral food challenges (OFCs) at the end of stage 1 (number of participants receiving omalizumab is noted within the bars).

ofat least 444 mg or at least 1044 mg of allergen protein. As indicated earlier, these are different from the original primary outcome of OUtMATCH,[1] as we believe that these thresholds aremore representative of accidental exposures encountered in the real-world setting.

Atleast 70% of omalizumab-treated participants were able to tolerate at least 444 mg and 1044 mg cumulative protein for peanut,egg, milk, and walnut] Cashew remained an outlier, with 66%and 49% of participants successful in tolerating at least 444 mg and at least 1044 mg of cumulative protein, respectively. Consideringthat most participants reacted to 10 mg of cashew protein (approximately 1/30th of a cashew) before treatment, toleratingat least 444 mg of protein (equivalent to 1.5 cashew nuts),or even lower amounts, represents a clinically significant responsefor at least two-thirds of individuals with cashew allergy.

Themost consistent predictor of success across all allergens was baseline tIgE level; however, this association was modest ($r = 0.25$; $q = 0.047$ for peanut CTD as a continuous variable). In patientswith chronic spontaneous urticaria and asthma, the associationof tIgE level and outcomes of omalizumab treatment has beenmixed. Some studies have suggested that a high tIgE level atbaseline is associated with successful response to omalizumab in chronic spontaneous urticaria[11-16] and asthma[17,18]; however, otherstudies have not.[19-24] We found that a higher pretreatment tIgElevel is associated with success across multiple outcomes as sessedvia univariate and decision tree analyses, including stage 1 food challenge thresholds as a continuous variable. This is in contrastto the findings of an oral immunotherapy study, in which lowertIgE level was associated with treatment success.[25]

The gains in predictive accuracy with the decision tree analyses that we conducted were modest, and they may be heavily dependent on the analysis population. The lower CTD results in participants with low tIgE level driving the poor NPV are based on studies with a small number of participants (as few as 7). We believe that this population is too small to draw meaningful conclusions, and larger studies are needed to evaluate the predictive strength of tIgE level in the real-world setting. Furthermore, tIgE levels can fluctuate over time owing to various individual exposures and comorbid disease activity. Together, these data suggest that the current markers are insufficient for predicting therapeutic response to omalizumab. Despite these limitations, tIgE levels could potentially be leveraged in practice to stratify patients into risk groups to preemptively identify the subset of patients who are most likely to respond successfully to omalizumab treatment. For instance, at the peanut CTD of 1044 mg or more, 92% of participants (22 of 24) with a baseline tIgE level of 1094 mg or higher (ie, the highest tIgE level quintile) were successful, whereas only 50% of participants (12 of 24) with a baseline tIgE level of 383 mg or lower (ie, the lowest tIgE quintile) were successful. This could help guide the potential need for food challenges to monitor therapeutic responses. More real-world studies are needed to confirm whether tIgE level is predictive of successful treatment.

Although omalizumab dosing frequency, sIgE level, and sIgE/tIgE ratio were predictors noted in the univariate analyses for some allergens, they did not remain important in the decision tree models using a multivariate approach. Because the dosing frequency is largely a function of tIgE level, the univariate tIgE

TABLE III. Baseline predictors of successful consumption of at least 1044 mg of peanut protein during the oral food challenge at the end of stage 1 (participants who received omalizumab)

Characteristic	Sample size	Failure (n = 34)	Success (n = 82)	*P* value*	*q* value†
Age (y), median (IQR)	116	8.5 (4.0-12.0)	6.5 (4.0-11.0)	.60	0.75
Pooled age group (y), no. (%)	116			.69	0.75
≤ 5		12 (28%)	31 (72%)		
6-11		12 (27%)	33 (73%)		
≥12		10 (36%)	18 (64%)		
Sex (male), no. (%)	116			.66	0.75
Female		13 (27%)	35 (73%)		
Male		21 (31%)	47 (69%)		
Dosing frequency, no. (%)	116			**.004**	0.051
Every 2 wk		13 (19%)	55 (81%)		
Every 4 wk		21 (44%)	27 (56%)		
Height (cm), median (IQR)	116	134 (107-152)	124 (103-144)	.35	0.52
Weight (kg), median (IQR)	116	30 (18-43)	25 (17-38)	.39	0.54
Body mass index, median (IQR)	116	16.90 (15.57-18.95)	16.79 (15.60-18.62)	.75	0.79
Target food,					
Cashew	116	26 (38%)	42 (62%)	**.012**	0.10
Egg	116	11 (22%)	40 (78%)	.10	0.35
Milk	116	6 (15%)	33 (85%)	**.019**	0.12
Walnut	116	17 (38%)	28 (62%)	.11	0.35
CTD (mg of protein)	116			.80	0.80
0		1 (50%)	1 (50%)		
1		1 (33%)	2 (67%)		
4		6 (33%)	12 (67%)		
14		8 (33%)	16 (67%)		
44		18 (26%)	51 (74%)		
Allergen specific SPT result (mm), median (IQR)‡	116	13.0 (8.5-21.0)	13.5 (9.0-18.5)	.60	0.75
Allergen-specific IgE level (kUA/L), median (IQR)§	116	68 (16-166)	78 (25-183)	.35	0.52
tIgE level (IU/mL), median (IQR)	116	563 (264-840)	764 (507-1212)	**.003**	0.051
Allergen-specific to tIgE ratio, median (IQR)	116	0.16 (0.05-0.30)	0.11 (0.04-0.21)	.26	0.50
BAT result, median (IQR)					
Unstimulated basophils	100	2.2 (1.1-4.2)	2.2 (1.3-4.1)	.33	0.52
fMLP level (1 M)	99	30 (15-40)	36 (20-52)	.20	0.46
Anti-IgE level (1 g/mL)	99	8 (5-37)	19 (6-44)	.22	0.46
0.001 g/mL	100	7 (3-20)	12 (3-29)	.65	0.75
0.01 g/mL	100	12 (5-32)	22 (4-51)	.34	0.52
0.1 g/mL	99	13 (7-27)	24 (5-56)	16	0.43
1 g/mL	99	9 (5-16)	17 (5-44)	.091	0.35
10 g/mL	100	17 (11-28)	30 (14-63)	**.025**	0.12
Area under the curve (AUC)	98	52 (30-96)	91 (25-184)	.18	0.45

Bolding denotes *P* value less than .05 or *q* value less than 0.05.
fMLP, *N*-formylmethionyl-leucyl-phenylalanine; *IQR*, interquartile range.
*Wilcoxon rank sum test; Pearson chi-square test; Fisher exact test.
†FDR correction for multiple testing.
‡SPT was performed with use of the Greer Pick device and extracts (Stallergenes Greer, Lenoir, NC). A positive result is defined as an SPT result greater than 3 mm.
§Allergen-specific IgE levels were measured by using ImmunoCAP (Thermo Fisher Scientific, Waltham, Mass). A positive result is defined as an allergen-specific IgE level higher than 0.35 kUA/L.

results raised the question of whether tIgE level is acting as a surrogate for dosing frequency. The results of the decision trees suggest that tIgE level is likely driving the results for dosing frequency within this cohort instead of the other way around. Yet, it is possible that dosing frequency was less predictive than tIgE level because analyses with continuous variables are generally more powerful than those with binary variables, as a result of which the model may prioritize the continuous variable over the binary variable. Ultimately, despite multiple analytic approaches, it is not possible to fully tease apart the individual contributions of these variables because of their interrelatedness in the dosing algorithm. Future studies investigating tIgE level as a predictive factor in stratified analyses in which the same dose of omalizumab was administered at a frequency of either every 2 weeks or every 4 weeks would be valuable.

Notably, the OUtMATCH study utilized a modified asthma-based dosing algorithm for omalizumab, in which the dosage and frequency are based on baseline weight and tIgE level. Analysis of level of free IgE following treatment indicated that this dosing approach effectively suppressed IgE to low levels associated with clinical improvement in asthma.[26,27] Others have demonstrated that complexes of omalizumab-bound IgE accumulate in the

TABLE IV. Multivariate decision tree predictions for peanut, cashew, success with at least 2 foods, and success with all 3 target foods with at least 444 mg or at least 1044 mg of food protein at the end of stage 1

Food (n)	Threshold (mg)	Successes	Total IgE* cut point	PPV (CV PPV)	NPV (CV NPV)
Peanut (n = 116)	444	89	—	89/116† (0.759)	—
	1044	82	268	80/105 (0.737)	9/11 (0.471)
Cashew (n = 67)	444	44	—	44/67† (0.558)	—
	1044	33	1065	18/21 (0.567)	31/46 (0.568)
≥2 foods (n = 116)	444	93	—	93/116 (0.795)†	—
	1044	84	220	83/109 (0.752)	6/7 (0.545)
All 3 foods (n = 116)	444	70	268	69/105 (0.637)	10/11 (0.643)
	1044	57	346	54/90 (0.494)	23/26‡ (0.514)

NPV is defined as the number of failures with an IgE level below the cut point divided by the number of individuals with an IgE level below the cut point. Em dash indicates food and/or threshold combinations for which no variables were selected after pruning. Analyses were also done for each of the other target foods and for at least 1 food, but no informative predictors emerged and thus have not been included in this table. The variables included in the analysis were weight, body mass index, age, sex, asthma, atopic dermatitis, rhinitis, dose frequency, dose amount, IgE ratio, tIgE level, SPT result, and allergen-specific IgE level (in the single-food analyses only).
CV PPV, Positive predictive value obtained through leave-1-out cross-validation; *IQR*, interquartile range; *PPV*, positive predictive value (defined as the number of successes with an IgE level above the cut point divided by the number of individuals with an IgE level above the cut point).
*tIgE level at baseline was the only consistently identified predictor of success among the variables included in the analysis, although its predictive accuracy is modest.
†PPV values are based on proportion of individuals who achieved the threshold when no variables were selected after pruning.
‡For all 3 foods at 1044 mg, 19 of the 26 individuals identified had a tIgE level below the cut point; 7 of 26 individuals identified had tIgE level above cut point but were identified as failures based on a secondary predictor.

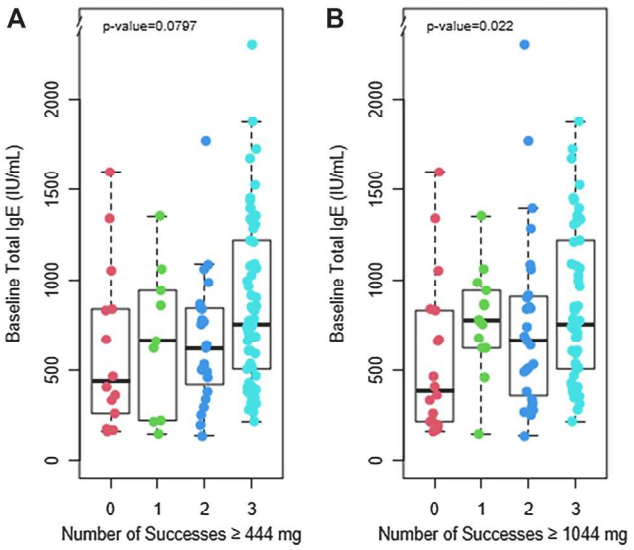

FIG 3. Count of successes by baseline total IgE level across the omalizumab-treated participants' 3 target foods per the clinically meaningful food protein thresholds of at least 444 mg (all foods) **(A)** and at least 1044 mg (all foods) **(B)** during oral food challenges (OFCs) at the end of stage 1. The result of the Kruskal-Wallis test comparing all categories was significant for the number of successes with a CTD of at least1044 mg (all foods); the result of subsequent pairwise comparison of 0 versus 3 foods was also significant ($P = .0086$ [**B**]). Because these were each separate analyses, the *q*-value correction was not applied.

body and maintain the ability to bind allergens. This interaction captures incoming antigens before their interaction with residual effector cell-bound FcεRI:IgE complexes, thereby inhibiting the subsequent activation of effector cells.[28,29] This mechanism may partially explain the increased food challenge threshold observed in patients with higher baseline tIgE levels, given their theoretic potential to form higher concentrations of such complexes. These potential mechanisms warrant further investigation. Other studies are exploring modifications to the omalizumab dosing regimen to determine whether such changes could provide greater benefits for individuals with food allergies.[30-32]

In addition to other baseline markers, coallergy to specific targetfoods appeared to influence the response to treatment for peanutwhen assessed as continuous CTDs. For example, allergy totree nuts such as cashew and walnut was negatively associated with CTD for peanut, whereas milk as a target allergen was positivelyassociated with higher CTD for peanut. These associations warrant further exploration to understand antigenic associationsbetween peanut and tree nuts,[33,34] as well as the potentialexistence of specific food allergy endotypes.

Lastly, we searched for correlates of response at the end of stage1 to identify biomarkers that a clinician might use to assess whethertreatment with omalizumab is successful without resortingto food challenges. Unfortunately, although treatment clearly suppressed both skin test and BAT responses, there were no consistent relationships with food challenge outcomes. Other mastcell markers such as metabolites may is of interest for future studies.

These analyses have limitations. The sample sizes for some allergens were small, and it is possible that some correlations detectedfor peanut would have also been demonstrated for other allergenswith larger numbers. The maximum number of assessed allergensfor each participant was capped at 3 foods (peanut plus 2 others that were selected by shared decision making with participants), which may introduce bias into the performed analyses of coallergen analyses. In addition to FDR *q* values, whichaccount for multiplicity, this hypothesis-generating analysispresents unadjusted *P* values to cast a wide net to identify potential predictors that need more study; these should be interpretedcautiously. However, this process lays the groundwork forfurther targeted studies to rigorously evaluate the validity of promising predictors and their potential clinical applications. AlthoughtIgE level emerged as the main biomarker associated withsuccess, we were confined to the parameters of the modified asthmadosing algorithm, which accommodates only a subset of patientswith food allergy with tIgE levels and weights that fall withinthe dosing table. If higher baseline tIgE level is an importantmarker of success, it will be important to understand treatmentdosing for patients with higher tIgE level than studied in the OUtMATCH trial. Indeed, this is an area of ongoing

TABLE V. Correlates of peanut CTD during the oral food challenge at the end of stage 1 (participants who received omalizumab)

Predictor	Sample size	Descriptive statistics	Spearman rank correlation		
			Correlation	*P* value	*q* value*
SPT result (mm) at end of stage 1, median (IQR)	116	7.8 (5.3-11.0)	–0.18	.058	0.17
Change in SPT result from baseline (mm), median (IQR)	116	–5.0 (–9.8 to –1.5)	–0.02	.84	0.90
Change in level of free IgE (IU/mL) at end of stage 1, median (IQR)	113	9.3 (6.3-12.3)	0.00	.97	0.97
BAT result at end of stage 1, median (IQR)					
Unstimulated basophils	90	1.93 (0.90-3.37)	–0.06	.56	0.65
fMLP level (1 μM)	93	34 (18-49)	0.08	.42	0.53
Anti-IgE level (1 μg/mL)	93	5 (2-10)	–0.16	.12	0.21
0.001 μg/mL	89	2.1 (1.1-3.6)	–0.09	.40	0.53
0.01 μg/mL	92	2.3 (1.4-4.2)	–0.20	.062	0.17
0.1 μg/mL	93	2 (1-5)	–0.18	.087	0.17
1 μg/mL	92	4 (2-8)	–0.18	.087	0.17
10 μg/mL	91	4 (2-12)	–0.21	**.045**	0.17
Area under the curve	86	13 (7-24)	–0.21	.050	0.17
Maximum decrease in BAT result	80	–27 (–59 to –7)	–0.22	**.048**	0.17
BAT result for dose at maximum decrease, no. (%)†	80		0.14	.22	0.34
0.001 μg/mL		9 (11%)			
0.01 μg/mL		22 (28%)			
0.1 μg/mL		12 (15%)			
1 μg/mL		5 (6.3%)			
10 μg/mL		32 (40%)			

Bolding denotes *P* value less than .05 or *q* value less than 0.05.
fMLP, *N*-formylmethionyl-leucyl-phenylalanine; *IQR*, interquartile range.
*FDR correction for multiple testing.
†Changes from baseline to stage 1 are computed within each BAT dose. The dose with the greatest decrease from baseline is the BAT dose at the maximum decrease. The value of that change is the BAT result at the maximum decrease. For participants whose BAT result increased from baseline to stage 1, the smallest increase is selected.

research.[30,35] Lastly, the relatively high rate of success at lower thresholds precluded us from adequately assessing the NPV of biomarkers (mostly tIgE level) yielded from the decision trees.

In conclusion, the evaluation of treatment success within the OUtMATCH study shows that at least 70% of participants with allergy to multiple foods are protected from small exposures to most foods following 16 to 20 weeks of omalizumab administration. Conventional allergy biomarkers, including SPT results, sIgE levels, and sIgE/tIgE ratios, were not useful in distinguishing those participants who had successful therapeutic outcomes, whether measured at baseline or following treatment. In this exploratory study, higher baseline tIgE level emerged as the most consistent predictor of response to therapy within the OUtMATCH data set. However, the predictive strength of tIgE was modest and potentially confounded with dosing frequency. This association should be confirmed in future studies, along with evaluation of its clinical utility, as it is not an ideal predictor of omalizumab outcome owing to its variable and, at best, moderate predictive power. This study highlights the necessity for identifying more reliable biomarkers to predict responses to omalizumab treatment, and at this time, the need to conduct oral food challenges in any patients seeking confirmation of protection against more than minor allergen exposures.

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Clinical implication: Total IgE level was the most consistent predictor of omalizumab response, but the strength of this association was modest.

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