

A phase II, randomized, double-blind, parallel-group, placebo-controlled oral food challenge trial of Xolair (omalizumab) in peanut allergy*To the Editor:*

Food allergy is the most common cause of anaphylaxis seen in emergency departments in the United States, and peanut allergy is the most common food provoking fatal or near-fatal reactions.¹⁻³ Currently, strict peanut avoidance and ready access to self-injectable epinephrine are the standard of care. Despite a growing awareness of food allergy, adherence to avoidance diets is very difficult, quality of life is markedly affected, and accidental ingestions remain common.⁴ Results from an earlier study suggested that humanized anti-IgE (Hu-901) might be effective for the treatment of food allergy.⁵ Hu-901 was not selected for further clinical development; however, omalizumab was approved for marketing in moderate to severe asthma. A phase II, multicenter, randomized, double-blind, placebo-controlled, parallel-group trial was therefore designed to assess the efficacy of omalizumab (Xolair; Genentech, South San Francisco, Calif), which had been approved by the US Food and Drug Administration for treatment of patients with moderate-severe asthma, in reducing the risk of peanut-induced allergic reactions. The study was designed to compare changes in peanut tolerability thresholds in subjects with proven peanut allergy who were treated with either omalizumab or placebo. Although the study intended to randomize 150 subjects, it was stopped early on the basis of the recommendation of the Data Safety Monitoring Committee because of the severity of 2 anaphylactic reactions that occurred during the qualifying oral food challenges (OFCs) before the administration of the study drug. Consequently, only 14 subjects reached the study's primary endpoint before the discontinuation of the trial. Despite the small number of subjects enrolled, some favorable trends in posttherapy peanut challenge thresholds were noted.

The primary objective of this study was to assess the efficacy of omalizumab in reducing the risk of peanut-induced allergic reactions by comparing the amount of peanut tolerated without symptoms before and after treatment. These thresholds were determined by double-blind placebo-controlled food challenge in subjects with peanut allergy treated with omalizumab compared with subjects treated with placebo. The OFC consisted of ingesting encapsulated peanut flour and placebo (wheat) flour on different days (1 day placebo [wheat] flour and 1 day peanut flour, with order determined at random). Doses of flour were 5, 15, 50, 100, and 250 mg during the initial qualification challenge and 5, 15, 50, 100, 250, 500, 1000, 1500, 4000, and 8000 mg during the posttherapy challenge, as tolerated. Subjects were eligible for the study if they were 6 to 75 years of age with histories of an

immediate peanut allergic reaction after the ingestion of a food containing peanuts, a positive skin prick test to peanut extract (Greer Laboratories, Lenoir, NC; wheal ≥ 3 mm), and/or detectable peanut-specific IgE (Phadia, Uppsala, Sweden; ≥ 0.35 kU_A/L), met the study drug dosing table eligibility criteria (serum pretreatment IgE level ≥ 30 to ≤ 1300 IU/mL and a body weight of ≥ 20 to ≤ 150 kg), and were able to perform reproducible spirometry maneuvers. Subjects were excluded if they could tolerate >250 mg peanut flour during the qualification OFC, reacted to any dose of placebo (wheat) flour at the qualification OFC, were taking specific immunotherapy at the time of study entry, had FEV₁ value $<80\%$ predicted or any clinical features of moderate persistent asthma (National Heart, Lung, and Blood Institute step 3 or above) despite current therapy, were being treated with greater than daily doses of inhaled corticosteroids (600 μ g fluticasone or equivalents for an adult or 400 μ g fluticasone or equivalents for a child) at the time of study entry, used oral or injected steroids within 30 days of the initial OFC, or had a history of brittle asthma or any other chronic medical condition.

Patients who reacted to ≤ 250 mg peanut and not wheat flour during the qualifying double-blind placebo-controlled food challenge were randomized 2:1 (omalizumab:placebo) to double-blind treatment for 20 to 22 weeks every 2 to 4 weeks with the study drug. The dose of study drug (omalizumab or placebo) administered was a minimum of 0.016 mg/kg/IgE (IU/mL) every 4 weeks; those requiring more than a 300-mg dose had their dose divided and given every 2 weeks. A second double-blind oral food challenge was performed at 24 weeks. The primary endpoint was a 3-level categorization threshold tolerability to peanut flour at week 24; 1000 mg, >1000 mg but <4000 mg, or ≥ 4000 mg. The protocol was approved by institutional review boards at participating institutions.

Before termination of the study, 100 subjects were screened, 45 subjects completed the initial qualifying OFC, 26 subjects were randomized to study drug (17 omalizumab and 9 placebo), and 14 subjects completed their posttherapy (24-week) OFC (9 omalizumab and 5 placebo). See Table E1 in this article's Online Repository at www.jacionline.org for symptoms induced. Mild to moderate adverse events were reported in both groups during the treatment phase—placebo, 88.9%, and omalizumab, 76.5%—and 2 mild adverse events were reported to omalizumab and none to placebo. Table I provides the demographics of subjects completing the posttherapy OFC, and Table II depicts the amount of peanut flour tolerated by each subject at the pretherapy and posttherapy OFCs. These limited data suggested an increase in tolerability to peanut flour in the omalizumab-treated versus placebo-treated subjects: 4 (44.4%) omalizumab-treated subjects versus 1 (20%) placebo-treated subject could tolerate ≥ 1000 mg peanut flour during an oral food challenge after 24 weeks of treatment with study drug ($P = .324$). A large proportion of subjects did not achieve the prespecified tolerability: 5 (55.6%) omalizumab-treated and 4 (80%) placebo-treated subjects experienced reactions at ≤ 1000 mg peanut flour. However, comparing the change from baseline in maximum tolerable peanut dose after 24 weeks of treatment, as depicted in Table II, there appears to be a greater shift in peanut tolerability in subjects treated with omalizumab for 24 weeks compared with placebo ($P = .054$; Friedman χ^2 test). The changes in total free IgE levels are also provided for omalizumab-treated subjects. In addition, on the basis of this relatively limited data set, the omalizumab safety profile in the population with peanut allergy is consistent with previous experience in the populations with asthma and allergic rhinitis.

TABLE I. Demographics of the 14 subjects completing the trial

Subject characteristics	Placebo (n = 5)	Omalizumab (n = 9)
Age (y), mean (SD)	26.6 (22.5)	16.3 (11.1)
6 to <13 years of age, n (%)	2 (40)	5 (56)
Sex, female, n (%)	1 (20)	5 (56)
Weight (kg), mean (SD)	56.7 (20.6)	56 (21.8)
FEV ₁ % predicted, mean (SD)	97.2 (9.0)	100.6 (10.2)
IgE (IU/mL), mean (SD)	367.6 (268.1)	197.0 (126.0)
Quartile 1-quartile 3	131-515	97-253

TABLE II. Change in peanut dose tolerability, per-protocol analysis, and change in free IgE in omalizumab-treated group

Placebo			Omalizumab				
Subject identification no.	Peanut flour (mg)		Subject identification no.	Peanut flour (mg)		Free total IgE (kU/L)	
	Wk 1	Wk 24		Wk 1	Wk 24	Wk 2	OFC 3
1107	15	50	1002	15	500	22.0	1.38
1419	15	50	1101	15	500	253.0	4.3
1502	50	50	1106	100	1500	40.0	2.44
1601	100	1000	1202	15	8000	406.0	3.04
1702	5	50	1402	50	500	216.0	11.35
Times increase from baseline: 4.07			1410	50	50	188.0	7.72*
			1501	100	1000	97.0	15.9
			1503	15	250	308.0	4.24
			1506	<5	1000	243.0	4.16
Times increase from baseline: 80.9							

*Value at week 20.

Currently, there are no approved forms of therapy for peanut allergy, although recent studies using oral immunotherapy have shown promise.^{6,7} This study was designed to determine whether omalizumab (given at a minimum dose of 0.016 mg/kg/IgE) is effective in preventing allergic responses to small amounts of peanut protein. While no firm conclusions can be drawn from these limited data, the results are consistent with findings of a similar anti-IgE preparation, HU-901⁵—that is, although the study was stopped early and most subjects on omalizumab did not reach the predefined study endpoints, omalizumab may increase the tolerability to peanut in a subset of patients with peanut allergy and may deserve further investigation.

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& Anaphylaxis Network, and the Wallace Research Foundation; has provided expert witness testimony on the subject of food allergy; is on the medical board of directors for FAAN; is a Dermatological Allergy Committee member for ACAAI; is a Study Section member for NIH HAI; and is on the reviewer board for the Journal and the FDA. G. Lack has received sponsorship from Phadia, Novartis, Danone Nutricia, Nestle, and DBV Technologies; has received research support from the Immune Tolerance Network/NIH, the National Peanut Board, the Food Standards Agency, the Medical Research Council, the Food Allergy Initiative, ALK-Abelló, Guy's & St Thomas' Charity, and Action Medical Research; and is a voluntary scientific advisor for the Anaphylaxis Campaign and the National Peanut Board.

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TABLE E1. Symptoms induced by OFCs

	Placebo Wk 1 (n = 5)	Placebo Wk 24 (n = 5)	Xolair Wk 1 (n = 9)	Xolair Wk 24 (n = 9)
Skin, n (%)	0	2 (40.0)	3 (33.3)	5 (55.6)
Nasal, n (%)	2 (40.0)	2 (40.0)	3 (33.3)	4 (44.4)
Chest, n (%)	1 (20.0)	1 (20.0)	0	2 (22.2)
Abdomen, n (%)	5 (100.0)	4 (80.0)	9 (100)	4 (44.4)