

ORIGINAL ARTICLE

Effect of Anti-IgE Therapy in Patients with Peanut Allergy

Donald Y.M. Leung, M.D., Ph.D., Hugh A. Sampson, M.D., John W. Yunginger, M.D., A. Wesley Burks, Jr., M.D., Lynda C. Schneider, M.D., Cornelis H. Wortel, M.D., Ph.D., Frances M. Davis, Ph.D., John D. Hyun, B.S., and William R. Shanahan, Jr., M.D., for the TNX-901 Peanut Allergy Study Group*

ABSTRACT

BACKGROUND

From the National Jewish Medical and Research Center, Denver (D.Y.M.L.); Mount Sinai School of Medicine, New York (H.A.S.); Mayo Clinic, Rochester, Minn. (J.W.Y.); Arkansas Children's Hospital, Little Rock (A.W.B.); Children's Hospital, Boston (L.C.S.); Clin-Quest, Marlborough, Mass. (C.H.W.); and Tanox, Houston (F.M.D., J.D.H., W.R.S.). Address reprint requests to Dr. Sampson at the Department of Pediatrics, Box 1198, Mount Sinai School of Medicine, 1 Gustave L. Levy Pl., New York, NY 10029-6574, or at hugh.sampson@mssm.edu.

*The members of the study group are listed in the Appendix.

N Engl J Med 2003;348:986-93.

Copyright © 2003 Massachusetts Medical Society.

Peanut-induced anaphylaxis is an IgE-mediated condition that is estimated to affect 1.5 million people and cause 50 to 100 deaths per year in the United States. TNX-901 is a humanized IgG1 monoclonal antibody against IgE that recognizes and masks an epitope in the CH3 region of IgE responsible for binding to the high-affinity Fcε receptor on mast cells and basophils.

METHODS

We conducted a double-blind, randomized, dose-ranging trial in 84 patients with a history of immediate hypersensitivity to peanut. Hypersensitivity was confirmed and the threshold dose of encapsulated peanut flour established by a double-blind, placebo-controlled oral food challenge at screening. Patients were randomly assigned in a 3:1 ratio to receive either TNX-901 (150, 300, or 450 mg) or placebo subcutaneously every four weeks for four doses. The patients underwent a final oral food challenge within two to four weeks after the fourth dose.

RESULTS

From a mean base-line threshold of sensitivity of 178 to 436 mg of peanut flour in the various groups, the mean increases in the oral-food-challenge threshold were 710 mg in the placebo group, 913 mg in the group given 150 mg of TNX-901, 1650 mg in the group given 300 mg of TNX-901, and 2627 mg in the group given 450 mg of TNX-901 ($P < 0.001$ for the comparison of the 450-mg dose with placebo, and P for trend with increasing dose < 0.001). TNX-901 was well tolerated.

CONCLUSIONS

A 450-mg dose of TNX-901 significantly and substantially increased the threshold of sensitivity to peanut on oral food challenge from a level equal to approximately half a peanut (178 mg) to one equal to almost nine peanuts (2805 mg), an effect that should translate into protection against most unintended ingestions of peanuts.

PEANUT ALLERGY IS CHARACTERIZED BY symptoms and signs after ingestion that may include nausea, vomiting, diarrhea, abdominal pain, urticaria, angioedema, bronchospasm, hypotension, loss of consciousness, and death.^{1,2} Although data from animals demonstrate that allergic reactions are mediated by antigen-specific IgE bound to high-affinity receptors for IgE (FcεR1s) on mast cells and basophils,^{3,4} non-IgE pathways for anaphylaxis exist, at least in mice,^{5,6} and direct clinical evidence of IgE involvement in peanut allergy in humans is lacking.

Approximately 1.5 million people in the United States have peanut allergy,^{7,8} 50 to 100 of whom die each year from unintended ingestion.^{9,10} Severe reactions can occur at any age,^{2,11} the previous reaction cannot be used reliably to predict the course of the next, and even the first reaction may be severe.^{1,11-13} Current treatment for peanut allergy is avoidance or rescue with epinephrine.^{12,14-16} Only a small minority of patients who are allergic to peanuts carry epinephrine, and even timely injection may not prevent death.^{8,11} Avoidance is extremely difficult,^{1,11,17} and the risk-benefit ratio for hyposensitization is unfavorable.¹⁸

TNX-901 is a humanized IgG1 monoclonal antibody against IgE that binds with high affinity to an epitope in the CH₃ domain, masking a region responsible for binding to both FcεR1s and low-affinity Fcε receptors (FcεRII, or CD23).¹⁹⁻²¹ In addition to inhibiting binding of IgE to mast cells and basophils, anti-IgE also markedly down-regulates the expression of FcεR1s on basophils^{22,23} and may inhibit allergen-specific activation of T cells through interference with the processing of antigen-presenting cells mediated by FcεRIIs or FcεR1s.²⁴

METHODS

PATIENTS

Patients 12 to 60 years of age with a history of peanut allergy manifested by urticaria, angioedema, lower respiratory tract symptoms, or hypotension were eligible for enrollment. Inclusion criteria were a serum total IgE level between 30 and 1000 IU per milliliter, good health, body weight within 20 percent of ideal, a positive skin-prick test to peanut and a negative skin-prick test to tuna oil, and no prior exposure to monoclonal antibodies. Eligible patients could not be pregnant. Any asthma was to be under control, with a forced expiratory volume in one second that was at least 80 percent of the predicted val-

ue. Systemic corticosteroids, beta-blockers, and acetylcholinesterase inhibitors were prohibited before screening and throughout the study, and aspirin, antihistamines, and antidepressants were prohibited for three days, one week, and two weeks, respectively, before skin testing or oral food challenge. Race was determined by the investigators.

STUDY DESIGN

This was a randomized, double-blind, placebo-controlled, dose-ranging study. Prospective patients underwent a screening physical examination and laboratory tests. Before enrollment, allergy to peanut was confirmed and the threshold for reactivity was established by a randomized, double-blind oral food challenge, as described below. Central randomization was performed in blocks of four per site. Patients were randomly assigned in groups of 28 and in a 3:1 ratio to receive 150 mg, 300 mg, or 450 mg of TNX-901 or placebo subcutaneously every four weeks for four doses. They then underwent a final oral food challenge with peanut flour within two to four weeks after the last dose. Enrollment at each dose level was completed before enrollment at the next level began. Every four weeks, blood and urine samples were obtained and patients were evaluated for adverse events. The final evaluation occurred eight weeks after the last dose (week 20).

The study was approved by institutional review boards at all participating centers, and all patients provided written informed consent. The data from all participating centers were sent to and monitored by ClinQuest, and all data were entered and locked before data analysis commenced. The data were analyzed by Abt Associates Clinical Trials. The study was designed by five of the investigators, three of whom had full access to the data. The sponsor did not limit the investigators' right to publish the results.

STUDY DRUG

Each dose of TNX-901 and placebo was supplied as a 150-mg lyophilized cake in a 5-ml clear-glass vial. A pharmacist reconstituted each cake with 1 ml of sterile water in an unblinded fashion and placed the solution in a syringe, which was masked to prevent study personnel from identifying the contents, for subcutaneous injection.

ASSESSMENT OF EFFICACY

The primary measure of efficacy was the change from base line in the threshold dose that induced

hypersensitivity to peanut flour, as assessed by an oral food challenge. The threshold dose was log-transformed (on a base 10 scale). Peanut flour was made by grinding equal portions of Valencia, runner, and Spanish peanuts (Greer Laboratories), the types used in virtually all peanut products consumed in the United States. The peanuts were defatted, and then various doses (1 mg to 2 g) were loaded into gel capsules. Matching placebo capsules were filled with similar amounts of cornstarch. For masking purposes, the capsules were rolled in tuna oil before administration.

The screening double-blind, placebo-controlled oral food challenge was administered on two days within a five-day period. At base line, spirometry was performed, intravenous access established, and continuous cardiac monitoring initiated. Vital signs were checked, chest auscultation was performed, and peak expiratory flow rates were monitored every 30 minutes during the food challenge and for at least 2 hours after the last dose or the abatement of any symptoms or signs. Patients were given increasing doses of placebo or peanut flour every 40 minutes until the principal investigator at each site judged that a definite reaction was occurring. To maximize safety and prevent severe reactions, the end point for the oral food challenge was the threshold dose for an allergic reaction. At screening, the initial dose was 1 mg, followed successively by 5, 10, 20, 50, 100, 200, 500, 1000, and 2000 mg of peanut flour or matching placebo capsules. Patients who could tolerate 2000 mg were considered to have had a negative test. To enter the study, each patient was required to have one positive and one negative result at screening, under the assumption that the positive result was to peanut. The final oral food challenge with peanut flour alone was initiated at 1 mg or 100 mg, depending on the screening threshold, and escalated to 4000 mg and then 8000 mg if tolerated. The dose escalation was terminated when an investigator believed there were clear-cut symptoms or signs of a hypersensitivity reaction, and the patient was then given activated charcoal slurry (Liqui-Char, Jones Pharma), which is believed to adsorb residual peanut protein in the stomach. Specific treatment protocols were followed in the event of asthma or other systemic reactions.

ASSESSMENT OF SERUM IgE, PEANUT-SPECIFIC IgE, TNX-901, AND ANTI-TNX-901 ANTIBODY LEVELS
Total IgE and free IgE (unbound by TNX-901), TNX-901, and anti-TNX-901 antibodies were measured

in blood samples with use of a modification of the enzyme-linked immunosorbent assays described for CGP 51901, the chimeric version of TNX-901.²⁵ Total peanut-specific IgE was measured by a fluorescence enzyme immunoassay (CAP-System, FEIA, Pharmacia Upjohn).²⁶

STATISTICAL ANALYSIS

The predefined primary efficacy measure was the change from base line in the log-transformed threshold dose of peanut flour that induced hypersensitivity. Since there were no clinical data on which to estimate the variability in this measure, the sample size was estimated on the basis of a dichotomous variable. Success was defined as an increase in the threshold dose of at least 0.9 log (by a factor of at least 7.9 or by three steps in the oral food challenge). Success constituted a secondary efficacy measure thought to be both clinically meaningful and unlikely to be due to placebo. Assuming a success rate of 80 percent for TNX-901 and 20 percent for placebo, a two-sided type 1 error rate of 0.05, a statistical power of 90 percent, and a multiple-comparison approach, 20 patients per group were required. To allow for a 5 percent dropout rate, the number was increased to 21 per group.

Safety and efficacy were analyzed on a predefined, modified intention-to-treat basis. Inclusion in the intention-to-treat analysis of efficacy required the receipt of at least one dose of study drug and values for base-line and repeated oral food challenges; safety analyses included any patient who received at least one dose of study drug. For the primary efficacy measure, pairwise comparisons of each TNX-901 group with placebo used Dunnett's test based on an analysis-of-covariance model with terms for treatment, site, base-line weight, base-line IgE levels, and base-line peanut-specific IgE levels. The proportion of patients who had an increase in the threshold dose of at least 0.9 log (success) was assessed by pairwise comparisons of each TNX-901 group with placebo with the use of Fisher's exact test, with adjustment for multiple comparisons. All reported P values are two-sided. No interim analysis was conducted.

RESULTS

STUDY POPULATION

The study was conducted between July 1999 and March 2002 at seven centers in the United States: 164 patients were screened, 84 patients under-

went randomization, and 81 completed the study. Two patients (one each in the 150-mg and 300-mg groups) were found to have had a positive placebo and a negative peanut challenge at screening. For both, a base-line threshold dose of 2000 mg (the highest dose administered at screening) was assigned, and the threshold dose was determined to be 100 mg at the final oral food challenge. In the 300-mg group, one patient discontinued the study on day 7 because of a myocardial infarction, and one stopped on day 43 because of a brain tumor. The efficacy analyses therefore included 82 patients. A total of 23 patients were randomly assigned to receive placebo, 19 to receive 150 mg of TNX-901, 19 to receive 300 mg of TNX-901, and 21 to receive 450 mg of TNX-901. One patient in the 450-mg group completed efficacy evaluations but withdrew consent before the final two visits. Base-line characteristics were similar among the groups (Table 1).

EFFICACY AND PHARMACODYNAMICS

Allergic reactions to peanut were generally well controlled by termination of the oral food challenge followed by the oral administration of charcoal and treatment with epinephrine, bronchodilators, antihistamines, and corticosteroids, as appropriate. One patient required overnight hospitalization for hypotension. The mean time from the final dose to the final oral food challenge was similar among the four groups (range, 21.2 to 24.5 days).

In all patients, the threshold of sensitivity to peanut was determined by a constellation of signs and symptoms typical of allergic reactions to food, at least one of which was judged to be moderate or severe in nature in all but 14 of the 166 challenges to peanut flour. Nausea, abdominal pain, vomiting, throat tightness, chest tightness, wheezing, persistent cough, rhinitis, conjunctivitis, pruritus, hives, and angioedema were among the most common

Table 1. Characteristics of the Patients Included in the Efficacy Analysis.

Characteristic	Placebo (N=23)	150 mg of TNX-901 (N=19)	300 mg of TNX-901 (N=19)	450 mg of TNX-901 (N=21)	Total (N=82)
Age (yr)					
Mean	34.4	34.9	28.3	31.6	32.4
Range	14–59	13–49	13–52	13–53	13–59
No. 12–17 yr of age	5	3	6	4	18
Sex (M/F)	10/13	11/8	12/7	12/9	45/37
Weight (kg)					
Mean	75.1	71.5	76.7	70.1	73.4
Range	59–99	45–114	43–100	45–95	43–114
Race or ethnic group (no.)					
White	20	16	19	20	75
Black	2	1	0	0	3
Hispanic	0	0	0	1	1
Asian	1	1	0	0	2
Other	0	1	0	0	1
Threshold sensitivity to peanut flour (mg)					
Mean	300.0	435.5	433.2	177.6	330.9
Range	1–2000	5–2000	5–2000	5–2000	1–2000
Serum IgE (IU/ml)					
Mean	251.3	349.8	205.1	286.7	272.5
Range	36–955	101–902	11–496	33–1017	11–1017
Serum peanut-specific IgE (U/ml)					
Mean	24.0	21.7	24.3	32.9	25.9
Range	0.34–100	0.34–100	0.34–100	0.69–100	0.34–100
Peanut-specific IgE (%)					
Mean	9.7	7.4	12.2	12.6	10.6
Range	0.15–42.7	0.14–30.5	0.20–34.5	0.47–30.4	0.14–42.7

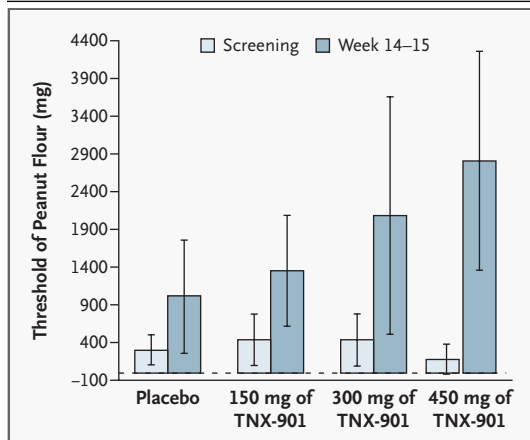


Figure 1. Mean Threshold Dose of Peanut Flour Eliciting Symptoms in Patients Receiving TNX-901 or Placebo.

The mean increase in the threshold of sensitivity, as compared with that in the placebo group, reached significance only in the 450-mg group ($P < 0.001$); however, results of the test for trend with increasing doses were significant ($P < 0.001$). I bars are 95 percent confidence intervals.

line in a dose-responsive manner. Although the increase, as compared with that in the placebo group, only reached statistical significance for the 450-mg group ($P < 0.001$) (Fig. 1), a strong trend was associated with increasing doses ($P < 0.001$). The proportion of patients who had an increase in the threshold of sensitivity of at least 0.9 log was greater in all the TNX-901 groups than in the placebo group, but again this difference was significant only in the 450-mg group ($P = 0.002$): 22 percent in the placebo group, 53 percent in the 150-mg group, 47 percent in the 300-mg group, and 76 percent in the 450-mg group (P for trend = 0.001). The proportions of patients in each group who tolerated a 0.5-, 1-, 2-, 4-, and 8-g challenge at screening and during the final oral food challenge, at week 14 to 15, are shown in Figure 2. In the placebo group, 4 percent of patients reached the highest level tested — 8 g — as compared with 0 percent of those in the 150-mg group, 21 percent of those in the 300-mg group, and 24 percent of those in the 450-mg group. Although pairwise comparisons with placebo of the proportions of patients who tolerated a given dose were not significant, significant trends with increasing dose were noted for the 4-g and 8-g threshold ($P = 0.02$ for both).

signs and symptoms that led to the termination of the oral food challenge.

The mean threshold of sensitivity to peanut at the final oral food challenge increased from base

Changes from base line in the log-transformed threshold dose correlated similarly with the dose

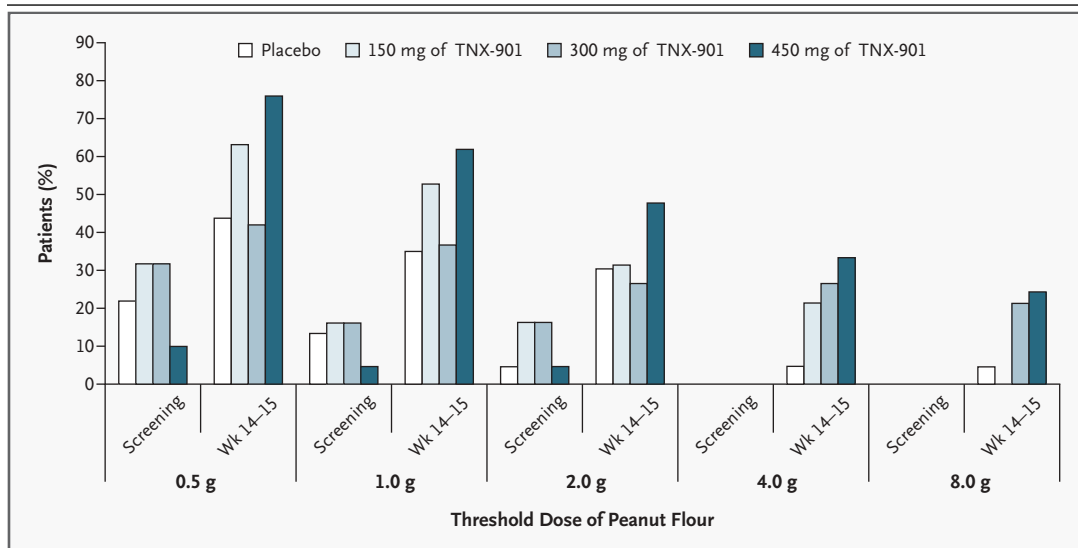


Figure 2. Percentage of Patients Who Tolerated Specified Dosing Thresholds during the Oral Food Challenge at Screening and Week 14 to 15.

Although pairwise comparisons with placebo did not reach statistical significance at any threshold level, the trend for increasing doses of TNX-901 at the 4-g and 8-g threshold levels was significant ($P = 0.02$ for both).

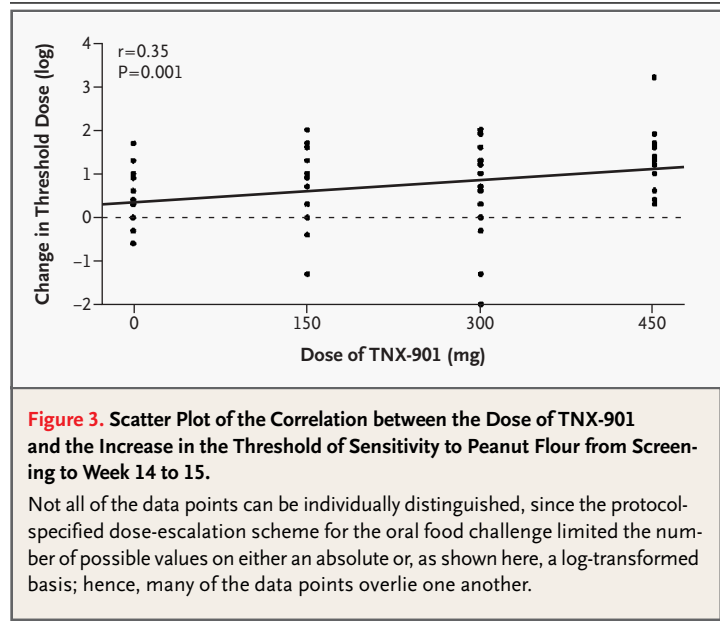
on an absolute basis in terms of milligrams of anti-IgE (Fig. 3), milligrams of anti-IgE per kilogram of body weight, and milligrams of anti-IgE per kilogram per total IgE level at base line, and these relations were statistically significant. Efficacy correlated less well with the dose on the basis of milligrams per kilogram per peanut-specific IgE level at base line and milligrams per kilogram per percent of total IgE that was peanut-specific at base line, and these correlations were not significant.

Trough drug levels were roughly dose proportional and reached steady state at week 12 (mean, 11.6 μg per milliliter in the 150-mg group; 32.2 μg per milliliter in the 300-mg group; and 57.5 μg per milliliter in the 450-mg group). Taking the trough level at week 12 as a measure of drug exposure, we found that the correlation between the change in the threshold dose and trough drug levels ($r=0.392$, $P<0.001$) was similar to that between threshold dose and the dose of TNX-901 ($r=0.381$, $P<0.001$).

Serum free IgE levels were measured every four weeks, just before each injection, and substantial reductions were obtained and sustained at all three doses of TNX-901. From base-line levels of 199.5 IU per milliliter in the placebo group, 262.0 IU per milliliter in the 150-mg group, 158.9 IU per milliliter in the 300-mg group, and 242.0 IU per milliliter in the 450-mg group, free IgE levels were 207.4 (an increase of 4.0 percent), 30.4 (a decrease of 88.4 percent), 17.0 (a decrease of 89.3 percent), and 16.6 (a decrease of 93.2 percent) IU per milliliter, respectively, at the end of week 4, just before the second injection, and similar reductions were observed throughout the dosing period. Eight weeks after the last dose of TNX-901, the last time point assessed, free IgE levels were still reduced from base line by 71.6 percent in the 150-mg group, 79.1 percent in the 300-mg group, and 88.7 percent in the 450-mg group.

SAFETY

TNX-901 was well tolerated. The incidences and spectrum of systemic adverse events and local adverse events were similar in the TNX-901 and placebo groups. The total number of systemic adverse events reported (range, 45 to 50 per group) and the number of patients who had such events (range, 15 to 19 per group) were similar among the four groups. Systemic adverse events that occurred more than once in a TNX-901 group are given in Table 2. With respect to local adverse events, injection-site reactions were noted in 13 to 14 patients in each group



and consisted primarily of erythema and, to a lesser extent, swelling and burning. All injection-site reactions were considered mild in nature except in one patient in the 450-mg group who had moderate erythema or edema on two occasions. There were no significant changes in the results of routine hematologic variables (including platelet count), serum chemical analyses, and urinalysis. There was no evidence of anti-TNX-901 antibodies in any patient.

DISCUSSION

In the absence of reliable epidemiologic data and given the impracticability of conducting a large, placebo-controlled trial in which episodes of anaphylaxis owing to accidental ingestions served as end points, we elected to use an increase in the amount of peanut flour required to elicit symptoms in an oral challenge as a valid substitute. A substantial increase in the threshold of peanut flour required to provoke symptoms should serve as a proxy for the level of protection against unintended ingestion. The double-blind, placebo-controlled oral food challenge is the standard for diagnosing food allergy and has been used as an efficacy end point in several studies.^{17,27-30} Although we discontinued the oral food challenge only when patients had symptoms or signs that typically precede more severe symptoms, this end point is not devoid of subjective interpretation, since some of these symptoms can be produced by anxiety. Reliable confirmation of an aller-

Table 2. Adverse Events Other Than Local Events That Occurred in More Than One Patient in a TNX-901 Group.

Adverse Event	Placebo (N=23)		150 mg of TNX-901 (N=19)		300 mg of TNX-901 (N=21)		450 mg of TNX-901 (N=21)	
	No. of Patients	No. of Events	No. of Patients	No. of Events	No. of Patients	No. of Events	No. of Patients	No. of Events
Diarrhea	1	1	4	5	1	1	1	2
Nausea	1	1	3	3	1	2	1	1
Vomiting	2	2	1	2	2	2	1	1
Fatigue	0	0	3	3	2	2	0	0
Fever	1	1	1	1	3	3	1	1
Food allergy*	6	7	4	4	7	7	5	6
Upper respiratory tract infection	7	8	7	12	10	12	3	4
Headache	3	4	4	5	2	2	2	2
Arthralgia	1	1	2	2	3	3	2	3

* Events related to food allergy were reported by the patient and were unrelated to oral food challenge. Reactions were due to exposure to a variety of foods, including tree nuts and seafood. Four food reactions occurred more than six weeks after the last dose of study drug: one each in the placebo, 300-mg, and 450-mg groups and two in the 150-mg group. Many of the food reactions were subjective in nature, and all were considered mild or moderate, except one event rated as severe in the placebo group. All reactions were treated expectantly or symptomatically. Approximately half the food reactions were considered mild and approximately half moderate in all groups except the 450-mg group, in which five food reactions were rated mild and only one was rated moderate.

gic response is not readily available, since plasma histamine (a marker of the allergic response) is very labile and difficult to measure,³¹ serum tryptase rarely increases during allergic reactions to peanuts,¹¹ and signs such as the heart rate are subject to anxiety on the part of the patient. A placebo effect was clearly seen. Two patients had negative peanut and positive placebo challenges at base line, with positive challenges to peanut at the final oral food challenge. In spite of these limitations, in experienced hands, the oral food challenge appears to be a reliable method of determining sensitivity to peanut in most patients. In general, the thresholds of sensitivity to peanut flour at screening and at the final evaluation were remarkably similar in the placebo group; only 5 of 23 patients had more than a two-step increase in the threshold.

Although the average amount of peanut consumed in an accidental exposure has not been accurately quantified, it is generally believed to be no more than one or two peanuts, or the equivalent of approximately 325 to 650 mg of peanut flour. The thresholds achieved in the 300-mg and 450-mg groups — 2083 and 2805 mg, respectively — are

equivalent to approximately six and eight peanuts, respectively, and should therefore provide substantial protection in most patients. In addition, 21 percent of patients in the 300-mg group and 24 percent of those in the 450-mg group were effectively tolerized and able to ingest at least 8 g of peanut flour (approximately 24 peanuts), the final dose in the food challenge, before having a reaction.

In patients with peanut allergy, there is currently no adequate treatment of or protection against the accidental ingestion of peanuts other than avoidance, although epinephrine modulates the reaction and can be lifesaving. Our clinical data confirm the direct role of IgE in peanut-induced hypersensitivity reactions and demonstrate that TNX-901, at a dose of 450 mg subcutaneously every four weeks, significantly increases the threshold of sensitivity to peanut antigen, as assessed by oral food challenge, to a level that should translate into at least partial protection against most unintended ingestions of peanut. Although these results are highly encouraging, TNX-901 is still an experimental drug, and approval for general use will require confirmation of these results in additional studies.

Supported by Tanox and in part by grants from the Peanut Board and the Peanut Foundation to Tanox and by grants from the National Institutes of Health National Center of Research Resources to the Mount Sinai School of Medicine (MO1 RR-00071) and to the Mayo Foundation (MO1 RR-585).

Drs. Leung, Sampson, Yunginger, and Schneider have reported receiving grant support from Tanox. Dr. Yunginger has also reported receiving grant support from Kimberly-Clark and lecture fees from Aventis Pharmaceuticals. Dr. Schneider has reported receiving grants from Baxter, Dyax, and Genentech. Dr. Burks has reported receiving

consulting fees from Unilever, Wyeth, and Monsanto; receiving a grant and holding stock options and related patents with SEER (formerly Panacea); and receiving grants from the Peanut Board, the National Peanut Foundation, Monsanto, and the Food Allergy Initiative. Dr. Davis, who was an employee of Tanox while the study was being carried out, is currently a consultant to Tanox and has stock options in Genentech. Mr. Hyun and Dr. Shanahan are employees of Tanox.

We are indebted to Sara Yankelev, M.S., and Roger Johnson, Ph.D., of Abt Associates Clinical Trials, Cambridge, Mass., for the statistical analyses.

APPENDIX

The TNX-901 Peanut Allergy Study Group consisted of the following investigators: A.W. Burks, Jr., L. Christie, and K. Althage, Arkansas Children's Hospital, Little Rock; H.A. Sampson, S.H. Sicherer, A. Nowak-Wegrzyn, and S.A. Noone, Mount Sinai School of Medicine, New York; L.C. Schneider, A. Alangari, and I. Borrás, Children's Hospital, Boston; J. Spergel, Children's Hospital of Philadelphia, Philadelphia; S.A. Tilles, Asthma, Inc., Seattle; D.Y.M. Leung, H.S. Nelson, E.D. Atkins, and J. Murray, National Jewish Medical and Research Center, Denver; and J.W. Yunginger, G. Volcheck, M. DeBolt, K.A. Bachman, and C. Wiginton, Mayo Clinic, Rochester, Minn.

REFERENCES

- Sicherer SH, Burks AW, Sampson HA. Clinical features of acute allergic reactions to peanut and tree nuts in children. *Pediatrics* 1998;102:131-2.
- Atkins FM, Steinberg SS, Metcalfe DD. Evaluation of immediate adverse reactions to foods in adult patients. I. Correlation of demographic, laboratory, and prick skin test data with response to controlled oral food challenge. *J Allergy Clin Immunol* 1985;75:348-55.
- Kinet JP. The high-affinity IgE receptor (Fc epsilon R1): from physiology to pathology. *Annu Rev Immunol* 1999;17:931-72.
- Long A. The nuts and bolts of peanut allergy. *N Engl J Med* 2002;346:1320-2.
- Miyajima I, Dombrowicz D, Martin TR, Ravetch JV, Kinet J-P, Galli SJ. Systemic anaphylaxis in the mouse can be mediated largely through IgG1 and Fc gamma RIII: assessment of the cardiopulmonary changes, mast cell degranulation, and death associated with active or IgE- or IgG1-dependent passive anaphylaxis. *J Clin Invest* 1997;99:901-14.
- Oettgen HC, Martin TR, Wynshaw-Boris A, Deng C, Drazen JM, Leder P. Active anaphylaxis in IgE-deficient mice. *Nature* 1994;370:367-70.
- Tariq SM, Stevens M, Matthews S, Ridout S, Twiselton R, Hide DW. Cohort study of peanut and tree nut sensitisation by age of 4 years. *BMJ* 1996;313:514-7.
- Sicherer SH, Munoz-Furlong A, Burks AW, Sampson HA. Prevalence of peanut and tree nut allergy in the US determined by a random digit dial telephone survey. *J Allergy Clin Immunol* 1999;103:559-62.
- Yocum MW, Butterfield JH, Klein JS, Volcheck GW, Schroeder DR, Silverstein MD. Epidemiology of anaphylaxis in Olmsted County: a population-based study. *J Allergy Clin Immunol* 1999;104:452-6.
- Bock SA, Munoz-Furlong A, Sampson HA. Fatalities due to anaphylactic reactions to foods. *J Allergy Clin Immunol* 2001;107:191-3.
- Sampson HA, Mendelson L, Rosen JP. Fatal and near-fatal anaphylactic reactions to food in children and adolescents. *N Engl J Med* 1992;327:380-4.
- Hourihane JO. Peanut allergy — current status and future challenges. *Clin Exp Allergy* 1997;27:1240-6.
- Vander Leek TK, Liu AH, Stefanski K, Blacker B, Bock SA. The natural history of peanut allergy in young children and its association with serum peanut-specific IgE. *J Pediatr* 2000;137:749-55.
- The use of epinephrine in the treatment of anaphylaxis. *J Allergy Clin Immunol* 1994;94:666-8.
- Sampson HA. Peanut allergy. *N Engl J Med* 2002;346:1294-9.
- Idem. Food allergy. 2. Diagnosis and management. *J Allergy Clin Immunol* 1999;103:981-9.
- Hallett R, Haapanen LAD, Teuber SS. Food allergies and kissing. *N Engl J Med* 2002;346:1833-4.
- Nelson HS, Lahr J, Rule R, Bock SA, Leung D. Treatment of anaphylactic sensitivity to peanuts by immunotherapy with injections of aqueous peanut extract. *J Allergy Clin Immunol* 1997;99:744-51.
- Chang TW. Pharmacological basis of anti-IgE therapy. *Nat Biotechnol* 2000;18:157-62.
- Davis FM, Gossett LA, Pinkston KL, et al. Can anti-IgE be used to treat allergy? *Springer Semin Immunopathol* 1993;15:51-73.
- Kolbinger F, Saldanha J, Hardman N, Bendig MM. Humanization of a mouse anti-human IgE antibody: a potential therapeutic for IgE-mediated allergies. *Protein Eng* 1993;6:971-80.
- MacGlashan DW Jr, Bochner BS, Adelman DC, et al. Down-regulation of Fc(epsilon)RI expression on human basophils during in vivo treatment of atopic patients with anti-IgE antibody. *J Immunol* 1997;158:1438-45.
- MacGlashan D Jr, McKenzie-White J, Chichester K, et al. In vitro regulation of Fc epsilon R1 alpha expression on human basophils by IgE antibody. *Blood* 1998;91:1633-43.
- van Neerven RJJ, van Rooijen CPAA, Thomas WR, de Boer M, Knol EF, Davis FM. Humanized anti-IgE mAb Hu-901 prevents the activation of allergen-specific T-cells. *Int Arch Allergy Immunol* 2001;124:400-2.
- Corne J, Djukanovic R, Thomas L, et al. Effect of intravenous administration of a chimeric anti-IgE antibody on serum IgE levels in atopic subjects: efficacy, safety, and pharmacokinetics. *J Clin Invest* 1997;99:879-87.
- Sampson HA, Ho DG. Relationship between food-specific IgE concentrations and the risk of positive food challenges in children and adolescents. *J Allergy Clin Immunol* 1997;100:444-51.
- Burks AW, Sampson HA. Double-blind, placebo-controlled trial of oral cromolyn in children with atopic dermatitis and documented food hypersensitivity. *J Allergy Clin Immunol* 1988;81:417-23.
- Halken S, Host A, Hansen LG, Osterballe O. Safety of a new, ultrafiltrated whey hydrolysate formula in children with cow milk allergy: a clinical investigation. *Pediatr Allergy Immunol* 1993;4:53-9.
- Sampson HA, Bernhisel-Broadbent J, Yang E, Scanlon SM. Safety of casein hydrolysate formula in children with cow milk allergy. *J Pediatr* 1991;118:520-5.
- Sampson HA, James JM, Bernhisel-Broadbent J. Safety of an amino acid-derived infant formula in children allergic to cow milk. *Pediatrics* 1992;90:463-5.
- Sampson HA, Jolie PL. Increased plasma histamine concentrations after food challenges in children with atopic dermatitis. *N Engl J Med* 1984;311:372-6.

Copyright © 2003 Massachusetts Medical Society.