

Response to “Effect of anti-IgE therapy in patients with food allergy”

We agree with Drs. Nicklas and Chowdhury¹ that present approaches to peanut allergy (avoidance and self-administered intramuscular epinephrine in the event of a reaction) are inadequate and that a therapeutic agent that can protect patients from food-induced anaphylaxis is greatly needed. Our recently reported phase 2 trial with TNX-901, an anti-IgE monoclonal antibody, in patients with peanut allergy was a proof-of-concept study that attempted to establish preliminary evidence that anti-IgE therapy might be protective in this indication.² We used the change in oral food challenge threshold sensitivity to peanut flour before and after a 4-month course of therapy as an end point. Based on the published article, the editorialists commented on several potential biases in the design and interpretation of this trial. We would like to both affirm some of the opinions expressed and address what we believe are some misinterpretations of our data and a lack of understanding of certain aspects of our trial.

Since our study was the first administration of TNX-901 to patients with peanut allergy, the study was designed as a dose-ranging study for safety reasons, with 3 dosing cohorts of 150, 300, and 450 mg (subcutaneously every 4 weeks) recruited sequentially after tolerability in the preceding cohort was first established. Ideally from an interpretation-of-efficacy standpoint, however, all cohorts would have been recruited in parallel rather than sequentially. Nevertheless, the study blind was maintained until all data from all 3 cohorts were entered into the database and the database for the entire study was locked.

Twenty-eight patients were recruited to each cohort (84 patients in total) and randomized 3 to 1 to receive TNX-901 or placebo. Patients 12 to 60 years of age with a history of peanut allergy who fulfilled all other inclusion and exclusion criteria were screened with a double-blind, placebo-controlled oral food challenge to confirm allergy to peanut and to establish the baseline sensitivity threshold to peanut flour for each patient. On 2 separate days within a 5-day period, patients were administered ascending doses of either peanut flour or placebo-filled capsules, beginning at a dose of 1 mg and then roughly doubling the dosage every 40 minutes until an allergic reaction was evident or a dose of 2,000 mg was tolerated. The dose at which a definite allergic reaction, in the opinion of the investigator, first occurred was defined as the sensitivity threshold, and if 2,000 mg was tolerated, then the patient was judged to be nonreactive to the test article.

The order of testing (peanut flour or placebo) was randomized, and patients and all study personnel were blinded to the order until the database was locked at the completion of the study. To be randomized for treatment, a patient had to have 1 positive and 1 negative challenge result, under the presumption that the positive challenge result would be to peanut and the negative result to placebo. Patients were then given 4 administrations of TNX-901 or placebo every 4 weeks and then underwent a final oral food challenge 15 to 30 days after the final dose of study drug. Originally, the final oral food challenge was designed as a double-blind, placebo-controlled challenge; however, due to slow recruitment during the first cohort, a belief in the relative objectivity of the test, and the inclusion of a placebo group that would allow for evaluation of impact of an open-label final challenge, the final challenge was changed to an open-label challenge with peanut flour only, which decreased the total number of challenges to either placebo or peanut flour in the study from 4 to 3 and shortened patient hospitalization by 1 day.

Our maintenance of the initial oral food challenge blind until the completion of the study proved to be an overzealous guarding of the study blind, because 2 patients were admitted to the study who subsequently were discovered to have had an initial negative challenge result to peanut and a positive challenge result to placebo, something that could have been avoided if the initial challenge blind (not the treatment blind) had been broken before randomization. However, it should be pointed out that admittance of these 2 patients biased the outcome against the drug. Both of these patients, 1 each in the 150- and 300-mg TNX-901 cohorts, were assigned the highest possible baseline threshold (2,000 mg), and both “reacted” in the final oral food challenge to 100 mg of peanut flour. For purposes of data analysis, each of these patients represented a highly negative drug effect, with a substantial decrease in threshold and increase in sensitivity to peanut after 4 months of TNX-901 administration. What these 2 patients demonstrate, however, is the potential for subjectivity in the oral food challenge. Administration of test article in an oral food challenge to an allergic individual is very anxiety provoking, and many of the symptoms that require discontinuation of the challenge may be produced by anxiety, such as nausea, vomiting, abdominal pain, diarrhea, tightness of the throat, difficulty swallowing, shortness of breath, and pruritus. Nevertheless, results in the placebo patients confirm the

reproducibility of the oral food challenge when administered by experienced investigators; only 5 of the 23 placebo patients demonstrated a greater than 2-step (approximately 4-fold) increase in threshold sensitivity during the study.

We readily admit that maintaining a blinded, randomized design for the final oral food challenge would have been a more rigorous design, but the blinded, placebo-controlled design of the study drug dosing groups allowed for both a control and an evaluation of the effects of an open food challenge at the final evaluation. Increases in threshold dose observed in the subcutaneous placebo group were modest, and increases in the higher-dose TNX-901 groups were robust: mean threshold sensitivity increased from 300 mg to 1,010 mg of peanut flour in the placebo group, and larger, dose-responsive increases were observed in the TNX-901 groups (from 178 to 2,280 mg in the 450-mg dose group).

The statement in the article that “the study was designed by five of the investigators, three of whom had full access to the data” was unfortunately truncated through the editorial process and can readily be misconstrued. No potential bias was introduced through premature unblinding. The data were not unblinded until all patients had completed the study, all data had been verified and entered into the database, and the database had been locked. All authors had access to the primary tables and figures, but only 3 authors had access to all of the raw data and analyses.

As pointed out by the editorialists and in the article, the predefined end point for the study was the log₁₀-transformed increase in peanut flour threshold. However, in the absence of clinical data on which to evaluate the variability of this end point, the study was powered on the basis of the secondary end point of “success,” which was defined as the proportion of patients achieving at least a 3-step increase (0.9 log₁₀ or 7.9-fold increase) in threshold sensitivity to peanut flour, assuming a success rate of 80% in a treatment group and 20% in the placebo group. For Figure 1, we thought that showing nontransformed thresholds would be more transparent than displaying log-transformed data. The *P* values given in this figure are for log₁₀-transformed increases, and unfortunately through the editorial process, this statement was dropped from the figure legend.

The editorialists comment that the proportion of patients achieving success was not significantly different between the 450-mg dose and placebo groups “when adjusted for the response observed in the placebo group.” We do not understand this comment. As stated in the article, “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 only reached significance in the 450-mg group (*P* = .002): 22% in the placebo group, 53% in the 150-mg group, 47% in the 300-mg group, and 76% in the 450 mg group (*P* for trend = .001). As also stated in the article, the Fisher exact test was used for comparison, with

adjustments for multiple comparisons to allow for comparison of each active treatment group with placebo.

The editorialists point out that there was a baseline imbalance in mean threshold dose of peanut flour across the treatment groups, ranging from 177.6 mg in the 450-mg dose group to 435.5 mg in the 150-mg dose group. The argument is made that since the lowest baseline threshold was in the only dose group to show a significant effect (the 450-mg dose group), the statistical significance might be due to this imbalance, presumably on the basis of a greater opportunity to improve. Although this hypothesis cannot be refuted or confirmed, the lower baseline threshold in the 450-mg dose group represents a more peanut-sensitive population, and this, we believe, should have an effect, if any, of biasing against a drug effect in this group.

The editorialists note that not all patients even in the highest-dose group (450 mg) were protected. Twenty-four percent in this dose group did not achieve at least a 3-step or 0.9 log₁₀ increase in threshold dose, and this same percentage had a threshold reaction to 500 mg of peanut flour (approximately 1.5 peanuts) after 4 months of TNX-901 use. The percentages of patients in the 450-mg group who achieved thresholds of 1,000, 2,000, 4,000, and 8,000 mg (approximately 24 peanuts) or greater were 67%, 48%, 33%, and 24%, respectively. The average unintentional ingestion is difficult to quantify but is thought to be on the order of 1 to 2 peanuts or fewer or approximately 325 to 650 mg of peanut flour.

In summary, these data suggest that a 450-mg dose of TNX-901 every 4 weeks for 4 doses would provide protection from accidental ingestion for approximately 50% to 75% of patients. Remarkably, at the final challenge in the 450-mg dose group, almost 25% of patients were able to tolerate at least 8,000 mg of peanut flour, the highest challenge dose administered, before having a reaction. An unintentional exposure to this much peanut flour is almost inconceivable. Whether a longer duration of therapy would provide protection to a greater proportion of patients is unknown. The half-life of mucosal mast cells induced by parasitic infection in rats has been reported to be 40 days.³ The half-life of human mast cells is unknown and may vary by tissue, whether resident or induced, and by cell phenotype. Efficacy of TNX-901 presumably depends on turnover of mast cells and basophils already sensitized with IgE to peanut antigen(s) at the initiation of therapy.

We agree with the editorialists that should TNX-901 or another anti-IgE therapy be ultimately proven effective for prophylaxis and approved, in the absence of a readily available and essentially infallible measure of protection it would be imperative that all treated patients continue to exercise avoidance and to carry an epinephrine pen.

The editorialists expressed a desire for further details regarding patient monitoring and the 2 serious adverse events described in the article. An inferior wall myocardial infarction

occurred on day 7 of the study, 6 days after the first administration of a 300-mg dose of TNX-901, in a 57-year-old man with hypertension and hypercholesterolemia. Angiography demonstrated 3-vessel coronary artery disease, and the patient successfully underwent 3-vessel coronary artery bypass surgery. A malignant brain tumor was diagnosed on day 43 of the study, approximately 2 weeks after receiving the second dosage of 300 mg of TNX-901, in a 53-year-old man with a 1-year history of progressive forgetfulness. The patient underwent partial removal of the tumor on day 50. Neither of these events was considered related to the study drug. There was no evidence of a drug effect on vital signs, monitored for 3 hours after each injection of study drug. Cardiac monitoring and pulmonary function testing if indicated were limited to the oral food challenges administered before initiation of treatment and 3 to 4 weeks after the final dose of study drug.

Due to the logistical difficulties, alluded to by the editorialists and in the original article, inherent in the execution of a natural history study evaluating allergic food reaction, we elected to conduct a study using oral food challenge threshold as the clinical end point. We believe that our study strongly suggests a potential for TNX-901 in preventing allergic reactions to peanut, but as we stated in our article, "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."

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