Original Article

Quantitative Assessment of the Safety Benefits Associated with Increasing Clinical Peanut Thresholds Through Immunotherapy

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What is already known about this topic? Immunotherapy for peanut allergy can increase the threshold of peanut protein to which peanut-allergic individuals react.

What does this article add to our knowledge? This article provides a quantitative assessment of the risk reduction of an allergic reaction associated with such increase in threshold.

How does this study impact current management guidelines? This study allows to better estimate the clinical benefit of immunotherapy for peanut allergy and equips health care providers with objective information for the management of peanut-allergic patients who underwent immunotherapy.

BACKGROUND: Peanut immunotherapy studies are conducted with the aim to decrease the sensitivity of patients to peanut exposure with the outcome evaluated by testing the threshold for allergic response in a double-blind placebo-controlled food challenge. The clinical relevance of increasing this threshold is not well characterized.

OBJECTIVE: We aimed to quantify the clinical benefit of an increased threshold for peanut-allergic patients.

METHODS: Quantitative risk assessment was performed by matching modeled exposure to peanut protein with individual threshold levels. Exposure was modeled by pairing US consumption data for various food product categories with potential contamination levels of peanut that have been demonstrated to be present on occasion in such food products. Cookies, ice cream, doughnuts/snack cakes, and snack chip mixes were considered in the risk assessment.

RESULTS: Increasing the baseline threshold before immunotherapy from 100 mg or less peanut protein to 300 mg peanut protein postimmunotherapy reduces the risk of experiencing an allergic reaction by more than 95% for all 4 food product categories that may contain trace levels of peanut residue. Further increase in the threshold to 1000 mg of peanut protein had an additional quantitative benefit in risk reduction for all patients reacting to 300 mg or less at baseline.

CONCLUSIONS: We conclude that achieving thresholds of 300 mg and 1000 mg of peanut protein by peanut immunotherapy is clinically relevant, and that the risk for peanut-allergic patients who have achieved this increased threshold to experience an allergic reaction is reduced in a clinically meaningful way. © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;■:■-■)

Key words: *Peanut allergy; Immunotherapy; Risk reduction; Efficacy*

Peanut allergy is a life-threatening, generally persistent food allergy and its prevalence has increased in the last decades to 1% to 2% of children in Western countries.[1,2] Strict avoidance of peanut consumption and use of rescue medication on occasions of unintentional peanut ingestion are the current ways of managing peanut allergy in the United States[3] and Europe.[4] Because of the wide distribution of peanut as a food ingredient in packaged foods and in restaurant and catering meals, complete avoidance is difficult and peanut-induced anaphylaxis occurs frequently.[5,6] Allergic reactions can be triggered by minute amounts of peanut protein as demonstrated by several studies that have evaluated individual thresholds and population threshold of peanut-allergic individuals.[7-10]

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Abbreviations used
DBPCFC- double-blind, placebo-controlled food challenge
NHANES- National Health and Nutrition Examination Survey
PAL- precautionary allergen labeling
ppm- parts per million (mg per kilogram of food)

Packaged food products do on occasion contain unintended allergen residue despite efforts to minimize cross-contact.[11,12] In these instances, food manufacturers use voluntary precautionary allergen labeling (PAL) such as "May Contain Peanut," "Processed on Shared Equipment with Peanut," "Processed in a Facility that Also Processes Peanut," or similar statements to communicate potential risk to allergic consumers; however, the wide use of such statements has caused some allergic consumers to ignore these advisory statements and consume the product.[12] Several retail surveys have been conducted to ascertain the concentrations of peanut residue, often expressed in parts per million (ppm, which is equal to mg of peanut residue per kg of food product), that may be present in packaged foods bearing PAL.[13-20] The reported concentration of peanut residue (ppm) can be used to calculate an exposure dose by multiplying by the consumed amount of the product that may contain the peanut residue (as illustrated in Table I).

Although these retail surveys do present a snapshot in time and varying levels may be present in these same food products that are produced on another day, peanut residue has occasionally been found in packaged food products at concentrations ranging generally from 0.63 to 1000 ppm peanut protein, which could present a risk for peanut-allergic consumers. Increasingly, allergic consumers are ignoring PAL or assigning potential risk to a product on the basis of the type of PAL present on the package label even though past retail surveys have indicated that the type of PAL does not correlate with the probability of the presence of allergen residue or the concentration of this residue.[12] The peanut content of prepackaged products in the US retail market including baked goods, candy/confections, cereal bars, frozen desserts, snack foods, and nutrition bars bearing PAL or no indication of peanut as an ingredient on the package label was surveyed recently, revealing that nutrition bars had the highest concentrations of unintended peanut residue (ie, peanut was not included as an ingredient in the food product formulation but was present because of cross-contact during production).[20] In bars surveyed in 2010 that did not contain peanut as an ingredient but that either had PAL regarding the potential presence of peanut (n = 159) or no mention of the potential presence of peanut (n = 49), the bars with detectable peanut residue (n = 14) ranged in concentration from 3.1 to 26,000 ppm peanut or 0.8 to 6500 ppm peanut protein based on an average of 25% protein in peanut as reported by the United States Department of Agriculture National Database for Standard Reference (Release 28),[21] with a mean of 496 ppm peanut protein and a median of 7.1 ppm peanut protein. It is important to note that nutrition bars bearing a "Unique Label" in this survey included peanut as a minor ingredient but also included a PAL statement for peanut or generically "nuts" that may include peanuts. Although 6500 ppm peanut protein was detected in a nutrition bar sample, the other bars with detectable peanut residue contained significantly lower concentrations of peanut residue (0.78-315 ppm peanut protein; mean, 33.7 ppm; median, 4.4 ppm). An earlier survey reported up to 4000 ppm peanut (1000 ppm peanut protein) in nutrition bars in the United States.[15] No other published retail surveys have indicated similarly high levels of peanut residue (>1000 ppm peanut protein) in other packaged food products, leading us to believe that the single sample containing 6500 ppm peanut protein may be an isolated event that does not reflect the typical range of peanut residue that may be present in packaged food products bearing PAL statements.

To illustrate what concentration levels expressed in ppm of peanut protein mean, the following example is given. A concentration of 496 ppm of peanut protein in a food product weighing 2 oz (59.1 g) corresponds to 496 × 1/1,000,000 × 59.1 = 0.0293 g or 29.3 mg peanut protein, which, in turn, corresponds to 117 mg of peanut or about 1/10 part of a large-kernel peanut such as Virginia. This example reflects only a selected amount of consumption and peanut protein concentration. An individual exposure dose will change depending on the amount of the food product that is consumed during an eating occasion. Quantitative risk modeling as discussed below is needed to describe exposure doses of peanut protein that peanut-allergic consumers may encounter.

Thus far no therapeutic intervention is available for peanut allergy. Several immunotherapy approaches are being clinically evaluated and show promise in terms of decreased sensitivity to peanut ingestion.[22,23] The end point for efficacy for such immunotherapy trials (oral,[24-27] sublingual,[23,28-30] or epicutaneous[31-33] immunotherapy) is an increase in an individual's threshold (eliciting dose) or in the cumulative reactive dose as tested in a double-blind, placebo-controlled food challenge (DBPCFC). To further determine the clinical relevance of reaching a higher threshold through immunotherapy, we have applied quantitative (probabilistic) risk modeling using food consumption data from the 2003-2010 National Health and Nutrition Examination Surveys (NHANES). We have calculated the probability of an allergic reaction for given threshold doses and quantified the protection against accidental exposure to unintended peanut residue that may be present in prepackaged food products upon an increase in threshold provided by immunotherapy.

METHODS

Input parameters for quantitative risk assessment

The quantitative risk assessment model incorporates a number of input variables to predict the allergenic risk associated with the exposure to residual peanut protein in food products.[20] The 2 primary input variables that were included in the assessment were the clinical threshold for peanut-allergic individuals and the exposure dose of peanut residue, as specified below.

Clinical threshold for peanut-allergic individuals. The potential decrease in a peanut-allergic individual's risk to accidental exposure to peanut protein in food products was assessed by a series of individual quantitative risk assessments in which the individual clinical threshold used in the model was held constant at 1, 3, 10, 30, 100, 300, or 1000 mg of peanut protein, reflecting the semi-logarithmic dosage increase recommended for DBPCFC.[34] These doses also represent the range of individual threshold doses found for peanut-allergic individuals on graded DBPCFC.[9] A meta-analysis study summarizing these studies show that the thresholds range from less than 1 mg to several grams of peanut protein, with the majority (82%) of interval-censored individuals (those with defined