2021

Predicted number of peanut-allergic patients needed to treat with epicutaneous immunotherapy (EPIT) to prevent one allergic reaction: A novel approach to assessing relevance

Benjamin C. Remington

Stef J. Koppelman

Todd D. Green

Gideon Lack

Graham Roberts

See next page for additional authors

Authors

Benjamin C. Remington, Stef J. Koppelman, Todd D. Green, Gideon Lack, Graham Roberts, and Dianne E. Campbell

Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY EAACI WILEY

DOI: 10.1111/all.14973

Predicted number of peanut-allergic patients needed to treat with epicutaneous immunotherapy (EPIT) to prevent one allergic reaction: A novel approach to assessing relevance

To the Editor,

Peanut allergy is a generally persistent,[1] sometimes life-threatening food allergy. With no treatments to date demonstrating the ability to cure peanut allergy, the focus has been on providing a level of protection against accidental exposure reactions through desensitization, defined as an increase in the reaction or eliciting dose (ED) threshold.[2–4] In a previously published quantitative risk assessment, modeling demonstrated an approximately 73–78% relative reduction per eating occasion in risk of reaction to peanut-contaminated packaged food products, with no change seen in the placebo group.[5] In this study, we sought to model the predicted number needed to treat (NNT) in order to prevent an allergic reaction when consuming peanut-contaminated food products in the UK, as well as the predicted NNT for the prevention of a moderate/severe allergic reaction (grade 2 or 3) as defined by a task force of the European Academy of Allergy and Clinical Immunology (EAACI) Food Allergy and Anaphylaxis Initiative.[6]

Population-based quantitative risk assessments using Monte Carlo simulations were utilized to model allergic reactions to peanut on a yearly basis (Figure 1; Table S1). Four primary inputs for the risk assessment were (1) the study-population dose distributions at baseline and 12-month double-blind, placebo-controlled food challenges (DBPCFCs) (with 95% confidence intervals), (2) consumption of a food product (frequency of consumption and amount), (3) concentration of peanut if the consumed product is contaminated, and (4) the proportion of peanut-allergic reactions by each severity group. United Kingdom consumption patterns were estimated for six food product categories (cookies, pastries, ice cream, salty snacks, rice-based meals, and chocolate [Table S2]) for which data are available and the total number of allergic reactions due to the unintended presence of peanut protein in one of these products was predicted on a yearly basis (365 days of potential exposure to peanut simulated for 1000 peanut-allergic individuals). Clinical data were utilized from a double-blind, placebo-controlled phase 3 study population of children, aged 4–11 years, treated with epicutaneous immunotherapy (EPIT) for 12 months with either a patch containing 250 μg peanut protein (DBV712 250 μg patch)or a placebo patch.[2,5] The concentration of peanut, if the consumed product is contaminated, was estimated from peanut protein concentrations in North American and European food retail surveys as previously summarized.[5] The simulation was repeated 50 times per study population to account for variability and uncertainties within input variables (Table S1).

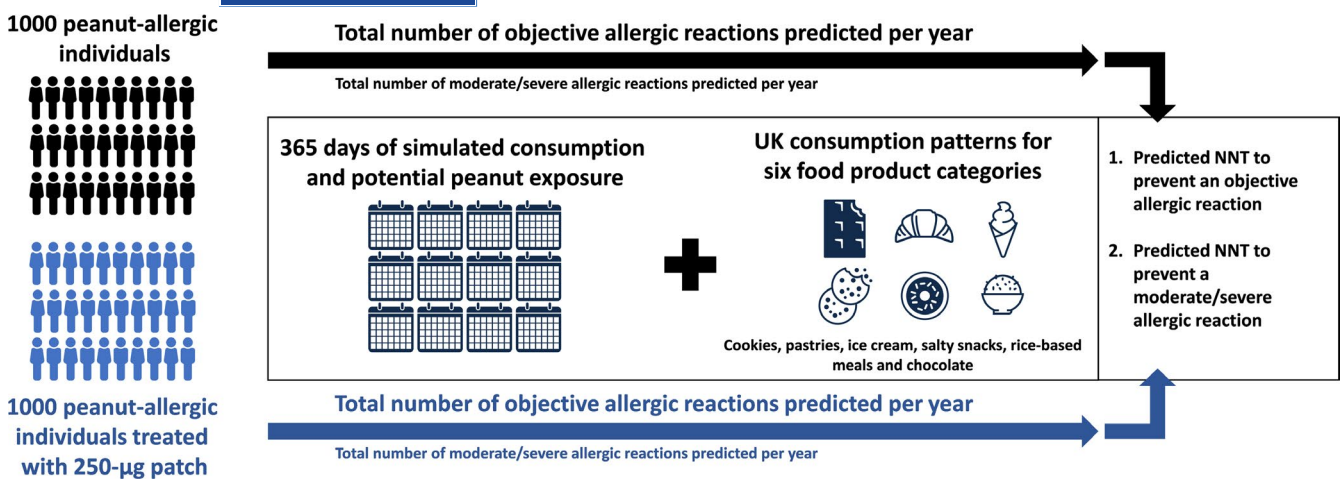

FIGURE 1 Visualization of the quantitative risk assessment model for NNT prediction

TABLE 1 Mean estimates of predicted NNT values from 50 repeated model runs. The predicted NNTs (Q25, Q75) for prevention of an objective allergic reaction and prevention of a moderate/severe allergic reaction (grade 2 or 3) as defined by a task force of the European Academy of Allergy and Clinical Immunology (EAACI) Food Allergy and Anaphylaxis Initiative are shown. These are calculated within a model using the unweighted averages for the rates of occurrence per allergic reaction (57.4%) presented in Table S3, as well as the minimum (38.7%) and maximum (70.7%) rates of occurrence of moderate/severe allergic reactions per allergic reaction in the included studies

Predicted NNT to prevent an objective allergic reaction	Mean estimate from model (Q25, Q75)
Using the DBV712250 µg baseline timepoint (T0) for NNT calculation	5.5 (5.9, 5.1)
Using the placebo 12-month timepoint (P12) for NNT calculation	3.9 (4.6, 3.4)

Predicted NNT to prevent a moderate/severe allergic reaction	Mean estimate using unweighted average frequency of occurrence from literature review (Q25, Q75)	Mean estimate from model if using minimum frequency of occurrence from literature review (Q25, Q75)	Mean estimate from model if using maximum frequency of occurrence from literature review (Q25, Q75)
Using the DBV712250 µg baseline timepoint (T0) for NNT calculation	9.4 (10.3, 8.9)	14.5 (15.4, 13.3)	7.9 (8.5, 7.2)
Using the placebo 12-month timepoint (P12) for NNT calculation	6.8 (7.4, 5.9)	10.2 (11.8, 9)	5.4 (6.3, 4.9)

The NNT in order to prevent one allergic reaction when consuming peanut-contaminated food products in the UK was then calculated.

The NNT to prevent a predicted moderate or severe reaction (as defined above)[6] was also calculated. In order to estimate the proportion of allergic reactions occurring due to accidental peanut consumption, which would result in a moderate and/or severe allergic reaction, a review of the relevant literature was performed. Of a total of 8 published studies identified, which reported episodes of peanut-allergic reactions by symptom classification, five studies were able to inform the population estimate of the proportion of all peanut-triggered allergic reactions reported that would result in moderate/severe symptoms (grade 2/3). The estimated unweighted mean for moderate and severe reactions was 57.4% (minimum 38.7%, maximum 70.7%). Further details can be found in Table S3.

Overall, the predicted risk reductions from treatment with DBV712250 µg for 12 months gave a NNT of 5.5 for prevention of an objective allergic reaction when consuming peanut-contaminated packaged food products (Table 1) and a NNT of 9.4 for prevention of a moderate/severe allergic reaction. By modeling using the baseline untreated population, 15.9% of the peanut-allergic individuals (159 of 1000 patients) were predicted to experience a mean total of 235 objective allergic reactions over the course of 1 year, with 136 moderate/severe reactions (Table S4). In contrast, the peanut-allergic population treated with the 12 months of DBV712 250 µg demonstrated a significant risk reduction, which resulted in 4.3% of individuals (43 of 1000 patients) predicted to experience a mean total of 53 objective allergic reactions over the course of 1 year, with 30 moderate/severe reactions. The model predicts an average of 182 objective allergic

reactions prevented per year for 1000 patients treated and prevention of106 moderate/severe reactions per 1000 patients treated.

Epicutaneous daily patch treatment with DBV712 250 µg (approximately 1/1000 one peanut) for 12 months has previously been shown to result in a statistically significant increase in desensitization in peanut-allergic children 4–11 years compared with placebo. Increasing the eliciting dose through desensitization should reduce an individual's risk of a reaction to an accidental exposure. It is well known that the severity of an allergic reaction to food ingestion is unpredictable and subject to influence of both known and unknown cofactors. The need for a universal severity grading system has previously been articulated, and while there is general agreement that early adrenaline use is preferred, there is lack of agreement about exactly which signs/symptoms should rise to that level of treatment globally. We used existing consensus EAACI guidelines to identify the moderate and severe allergic reactions where such treatment may be appropriate, acknowledging that this is a decision point that is likely best individualized based on an individual's history and other risk factors. Acknowledging the above caveats and limitations of this literature-based analysis, here we sought to estimate the NNT associated with DBV712 250 µg in order to prevent the most clinically concerning allergic reactions (those rising to the level of moderate/severe and need for adrenaline) based on clinical experience reported from the literature. It is worth noting that the NNTs we have estimated compare favorably with those derived from clinical trials involving other allergic diseases, for example, prevention of asthma exacerbations/hospitalizations with omalizumab and mepolizumab.[7–9] It should be noted that a potential limitation to the modeling is that it was based upon treatment response to DBV712 in a population with an ED threshold at baseline to 300 mg or less, and may be different for children with significantly higher pre-treatment threshold. Another potential limitation affecting generalizability of the model is that the consumption data do not come from a selected peanut-allergic population, though it has been recently shown in a specific food consumption survey that intake levels of the general population represent those of food allergic patients.[10] In addition, we rely on modeling data here because of the relatively small sample size and limited time frame of the phase 3 study, but the findings raise important "real-life" questions for further investigation.

In conclusion, the NNTs in this study predict a substantial risk reduction for allergic reactions, for both reactions of any severity as well as for moderate/severe allergic reactions, among peanut-allergic children after 12 months of EPIT with DBV712 250 µg. The NNT is important in assessing the benefit/risk profile of a potential therapy, and our results support the potential real-world clinical relevance of this investigational immunotherapy.

FUNDING INFORMATION

This study was funded by DBV Technologies.

CONFLICT OF INTEREST

Dr. Remington reports grants, personal fees, and non-financial support from DBV Technologies, during the conduct of the study; non-financial support from ILSI Europe, outside the submitted work; and is an adjunct faculty member of the University of Nebraska. Dr. Koppelman reports grants, personal fees, and other from DBV Technologies and grants from University of Nebraska, during the conduct of the study; personal fees and other from DBV Technologies, outside the submitted work; and is an adjunct faculty member of the University of Nebraska. Dr. Green reports other from DBV Technologies, during the conduct of the study. Dr. Lack reports grants from National Institute of Allergy and Infectious Diseases (NIAID, NIH), other from Food Allergy & Research Education (FARE), MRC & Asthma UK Centre, UK Dept of Health through NIHR, National Peanut Board (NPB), and The Davis Foundation, and grants from UK Food Standards Agency (FSA), during the conduct of the study; and personal fees and other from DBV Technologies, other from Mighty Mission Me, personal fees from Novartis, Sanofi-Genzyme, Regeneron, and ALK-Abello, and personal fees and other from Lurie Children's Hospital, outside the submitted work. Dr. Roberts reports acting as a consultant to DBV during the conduct of the study. Dr. Campbell reports personal fees from DBV, during the conduct of the study; and grants from National Health and Medical Research Council of Australia, personal fees from AllerGenis, and other from Nestle Health Science and from Westmead Fertility Centre, outside the submitted work.

Benjamin C. Remington[1,2]
Stef J. Koppelman[1,3]
Todd D. Green[3,4]
Gideon Lack[5,6,7]
Graham Roberts[8,9,10]
Dianne E. Campbell[3,11]

[1]*Food Allergy Research and Resource Program, University of Nebraska, Lincoln, NE, USA*
[2]*Remington Consulting Group BV, Utrecht, The Netherlands*
[3]*DBV Technologies, Montrouge, France*
[4]*UPMC Children's Hospital of Pittsburgh, Pittsburgh, PA, USA*
[5]*Paediatric Allergy Group, Department of Women and Children's Health, School of Life Course Sciences, King's College London, London, UK*
[6]*Peter Gorer Department of Immunobiology, School of Immunology & Microbial Sciences, King's College London, London, UK*
[7]*Children's Allergy Service, Guy's and St. Thomas' NHS Foundation Trust, London, UK*
[8]*NIHR Southampton Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust, Southampton, UK*
[9]*Clinical and Experimental Sciences and Human Development in Health, Faculty of Medicine, University of Southampton, Southampton, UK*
[10]*The David Hide Asthma and Allergy Research Centre, St Mary's Hospital, Isle of Wight, UK*

[11]*Department of Allergy & Immunology, Children's Hospital at Westmead, Sydney, NSW, Australia*

Correspondence
Benjamin C. Remington, Food Allergy Research and Resource Program, University of Nebraska, Lincoln, NE, USA.
Email: bremington2@unl.edu

ORCID

Benjamin C. Remington https://orcid.org/0000-0001-5450-8334
Stef J. Koppelman https://orcid.org/0000-0001-7995-1754
Todd D. Green https://orcid.org/0000-0002-2586-3625
Gideon Lack https://orcid.org/0000-0001-7350-4021
Graham Roberts https://orcid.org/0000-0003-2252-1248
Dianne E. Campbell https://orcid.org/0000-0002-0907-6963

REFERENCES

1. Nwaru BI, Hickstein L, Panesar SS, et al. Prevalence of common food allergies in Europe: a systematic review and meta-analysis. *Allergy*. 2014;69:992-1007.
2. Fleischer DM, Greenhawt M, Sussman G, et al. Effect of epicutaneous immunotherapy vs placebo on reaction to peanut protein ingestion among children with peanut allergy: the PEPITES randomized clinical trial. *JAMA*. 2019;321:946-955.
3. Kim EH, Yang L, Ye P, et al. Long-term sublingual immunotherapy for peanut allergy in children: clinical and immunologic evidence of desensitization. *J Allergy Clin Immunol*. 2019;144:1320-1326.
4. Vickery BP, PALISADE. AR101 oral immunotherapy for peanut allergy. *N Engl J Med*. 2018;379:1991-2001.
5. Remington BC, Krone T, Kim EH, et al. Estimated risk reduction to packaged food reactions by epicutaneous immunotherapy (EPIT) for peanut allergy. *Ann Allergy Asthma Immunol*. 2019;123:488-493.
6. Muraro A, Fernandez-Rivas M, Beyer K, et al. The urgent need for a harmonized severity scoring system for acute allergic reactions. *Allergy*. 2018;73:1792-1800.
7. Busse WW, Morgan WJ, Gergen PJ, et al. Randomized trial of omalizumab (anti-IgE) for asthma in inner-city children. *N Engl J Med*. 2011;364:1005-1015.
8. Humbert M, Beasley R, Ayres J, et al. Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE. *Allergy*. 2005;60:309-316.
9. Ortega HG, Liu MC, Pavord ID, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. *N Engl J Med*. 2014;371:1198-1207.
10. Blom WM, van Os-Medendorp H, Bijlsma S, et al. Allergen risk assessment: food intake levels of the general population represent those of food allergic patients. *Food Chem Toxicol*. 2020;146:111781.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.