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Title:

Improvements in Eliciting Dose Across Baseline Sensitivities Following 12 Months of Epicutaneous Immunotherapy (EPIT) in Peanut-Allergic Children Aged 4 to 11 Years

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Dianne E. Campbell, Todd D. Green, and Romain Lambert are employees of DBV Technologies. David M. Fleischer has served as a consultant for DBV Technologies, Allergenics, Aquestive, Aravax, Genentech, Nasus, and Intrommune, and receives royalties from UpToDate. Edwin H. Kim reports consultancy with Aimmune Therapeutics, DBV Technologies, AllerGenis, Allakos, Ukko, ExVivo Labs and Vibrant America; clinical medical advisory board membership with DBV Technologies; and receipt of grant funding from the National Institutes of Health (NIH)/National Institute of Allergy and Infectious Diseases (NIAID), the NIH/National Center for Complementary and Integrative Health (NCCIH), Food Allergy Research & Education (FARE), and the Wallace Research Foundation. Matthew Greenhawt is supported by grant #5K08HS024599-02 from the Agency for Healthcare Research and Quality; is an expert panel and coordinating committee member of the NIAID-sponsored Guidelines for Peanut Allergy Prevention; has

served as a consultant for the Canadian Transportation Agency, Thermo Fisher, Intromune, and Aimmune Therapeutics; is a member of physician/medical advisory boards for Aimmune Therapeutics, DBV Technologies, Sanofi/Genzyme, Genentech, Glaxo Smith Kline, Nutricia, Kaleo Pharmaceutical, Nestle, Aquestive, Allergy Therapeutics, Allergenics, Aravax, Protax, and Monsanto; is a member of the scientific advisory council for the National Peanut Board; has received honorarium for lectures from Thermo Fisher, Aimmune Therapeutics, DBV Technologies, Before Brands, multiple state allergy societies, the American College of Allergy Asthma and Immunology, the European Academy of Allergy and Clinical Immunology; is an associate editor for the Annals of Allergy, Asthma & Immunology; and is a member of the Joint Taskforce on Allergy Practice Parameters.

Clinical Implications:

Post-hoc analyses presented herein evaluate eliciting dose changes following EPIT treatment in clinical trials in a more insightful way than a binomial endpoint approach allows.

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For the large population of children with peanut allergy, treatment options are limited. Several potential approaches to food allergy immunotherapy are either approved for restricted use by the US Food and Drug Administration (FDA), offered outside of a regulatory pathway, or are in various stages of clinical development.¹⁻³ Regardless of the approach, these therapies aim to desensitize patients to peanut while supplementing the current standard of care: vigilant avoidance and readiness to manage allergic reactions from unintended ingestion. While desensitization is broadly defined as an increase in the reaction threshold seen during active therapy,⁴ this has been measured in various ways and has relied on the diagnostic gold standard: the double-blind, placebo-controlled food challenge (DBPCFC). FDA guidance from 2016 further emphasized the importance of using DBPCFC endpoints as outcome measures by monitoring pre- to post-therapy change in eliciting dose (ED).⁵ Changes in ED or successfully consumed/tolerated dose (TD) have been used as a marker of the degree of desensitization achieved following food immunotherapy.

Peanut allergy immunotherapy clinical trials to date have stipulated predefined, binary endpoints (an increase in either ED or TD to a specific level) be achieved for a patient to be designated a “responder” to treatment. These threshold endpoints vary across studies, without universal agreement as to what constitutes a meaningful response in these patients, many of whom remain allergic.⁶ This binary classification risks dismissing significant increases in ED/TD attributable to active therapy that do not meet the predefined threshold, when in fact potentially clinically meaningful gains may represent a more comprehensive vantage regarding therapeutic benefit. Real-world change is often viewed on a continuum and not in terms of a binary response. Indeed, qualitative research involving caregivers of peanut-allergic children has indicated that any ED/TD increases may be clinically meaningful and meet preference-sensitive care goals of therapy.^{7,8}

Epicutaneous immunotherapy (EPIT) in peanut-allergic children with a 250- μ g peanut patch has been shown to be superior to placebo in desensitizing patients to peanut protein in both phase 2 and 3

clinical trials following 12 months of treatment.^{3,9} In PEPITES, the pivotal phase 3 EPIT efficacy and safety trial, a statistically significant difference ($P<0.001$) between active versus placebo response was observed in children aged 4 to 11 years using responder criteria requiring patients to move either from an ED of ≤ 10 mg to ≥ 300 mg or from >10 mg to ≥ 1000 mg.³ The lower bound of the 95% confidence interval (CI) of the difference between placebo and active response rates (difference between treatment arms 21.7%, 95% CI: 12.4-29.8) narrowly missed a prespecified lower bound threshold of 15% agreed upon with the FDA, though this margin holds unclear clinical significance for treating peanut-allergic patients.³ As previously reported, post-hoc analysis of the results demonstrated that 62.6% of participants in the active arm versus 28% in the placebo arm experienced an increased ED at Month 12 compared to baseline, while 6.7% of active versus 33.9% of placebo subjects experienced a decrease³, equating to a greater than 4-fold odds of improving with treatment (odds ratio [OR]=4.3; 95% CI: 2.7-7.0) and greater than 7-fold odds of worsening with placebo (OR=7.1; 95% CI: 3.8-13.4). Moreover, though both groups entered the phase 3 trial at similar sensitivities (entry geometric mean ED of 70.4 mg and 78.1 mg, respectively), at exit, the active group increased in geometric mean ED by nearly 4-fold (282.0 mg) while the placebo group remained relatively unchanged (79.3 mg) in the intent-to-treat population. Given the evidence of response in a considerable proportion of PEPITES patients who underwent treatment, and to better highlight response to EPIT, we conducted a post-hoc analysis of ED at 12 months according to baseline ED. For each baseline ED, geometric mean ED at 12 months was described and compared between active and placebo groups using a two-sample t-test on log-transformed data while the proportion of subjects achieving an ED ≥ 1000 mg was described and compared using Fisher's exact test. 1000 mg was chosen as an important ED which could be applied across the whole study population, and is also a key outcome of interest of the open-label extension of the PEPITES study (PEOPLE). The full statistical analysis for the PEPITES study has been detailed elsewhere.³

As seen in Figure 1, for each entry ED established through DBPCFC, patients treated daily for 12 months with the 250- μ g peanut protein patch were able to achieve 2- to 6-fold greater ED increases vs. placebo, with statistically significant (3 mg, $P=0.03$; 10 mg, $P=0.01$, 30 mg-300 mg, all $P<0.001$) differences observed at all entry EDs ≥ 3 mg. In addition, at 12 months, the geometric mean ED ratio between active and placebo groups was 5.3 (95% CI: 2.1-13.3) in those with a baseline ED ≤ 10 mg and 3.3 (95% CI: 2.4-4.5) in those with a baseline ED >10 mg. As shown in Figure 2, the raw proportion of patients in the treatment group who were able to achieve an ED ≥ 1000 mg after 12 months was higher compared to placebo for every entry ED of 3 mg or greater. Furthermore, no placebo-treated patients with an entry ED ≤ 10 mg were able to reach this endpoint.

This post-hoc analysis demonstrated significant response to treatment in a larger proportion of patients than was elucidated by the trial's binary endpoints. Given the trial design, recruitment did not employ a stratified sampling frame that would enrich power to $\geq 80\%$ for each ED entry point. However, we still noted global trends occurring with ED increases and wished to further examine the ED improvements across the various ED points at study baseline. Despite the sample size not being designed to evaluate such sub-group stratification, statistically significant differences in ED were still seen after 12 months of treatment for patients who entered the study at every ED ≥ 3 mg. There was a trend in the same direction for those patients entering at an ED of 1 mg, though these findings are limited by insufficient power to find a difference, if one truly existed.

Clinical trial endpoints to date have been chosen with imperfect understanding of preference-sensitive care choices and goals relative to what clinically meaningful may represent to patients and parents, or what is accepted by clinicians.⁶ Indeed, both qualitative and patient-preference data support a more individualized view of what clinically meaningful change represents, in that improvement may not always be viewed in terms of a specific threshold cut-off that may be achieved or eclipsed in a study endpoint, and that a continuum of acceptable responses may exist. Patients and caregivers express their

treatment goals in terms of a “safeguard, described as a buffer” against allergic reactions from unintentional peanut ingestion.⁷ Quantitative risk assessment (QRA) analysis offers one such alternative way to assess whether such treatment goals are likely to be met. Previously published QRA modeling has suggested that, based on their ED changes in PEPITES, patients in the active arm are predicted to experience a 73%-78% reduction in the relative risk of an allergic reaction per eating occasion following exposure to a variety of possibly peanut-contaminated packaged goods, with no change in risk seen in the placebo group.⁴

More data are needed to fully understand response to EPIT, including time to achieve response, floor/ceiling effects relative to gain from entry ED, and a consensus definition of what constitutes clinically meaningful change for EPIT relative to a diverse group of stakeholders. The FDA has discussed the importance of evaluating ED changes following treatment,⁵ and the post-hoc analyses presented here may do this in a more insightful way to facilitate the understanding of changes after 12 months of EPIT, and better highlight these changes given they were reflective of significant improvements in quality of life.⁸ The definition of “clinically meaningful” may in fact differ based on the therapy modality, the child’s age, and the family context. Continued work is needed to be able to measure the individualized impact of treatment response that may better refine clinical trial endpoints.

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Figure Titles/Legends:

Figure 1: Comparison of Geometric Mean ED at Month 12 According to Baseline ED

Legend: Comparison of the geometric mean eliciting dose at the exit double-blind, placebo-controlled food challenge after 12 months of treatment with either 250- μ g peanut patch or placebo, based on their entry ED. Asterisks denote a statistically significant change between arms with $P < 0.05$.

Figure 2: Comparison of Proportion of Subjects with ED ≥ 1000 mg at Month 12 According to Baseline ED

Legend: Comparison of subjects reaching an ED ≥ 1000 mg at the exit double-blind, placebo-controlled food challenge after 12 months of treatment with either 250- μ g peanut patch or placebo, based on their entry ED. Asterisks denote a statistically significant change between arms with $P < 0.05$.

Figure 1

Geometric Mean ED at Month 12 According to Baseline Sensitivities

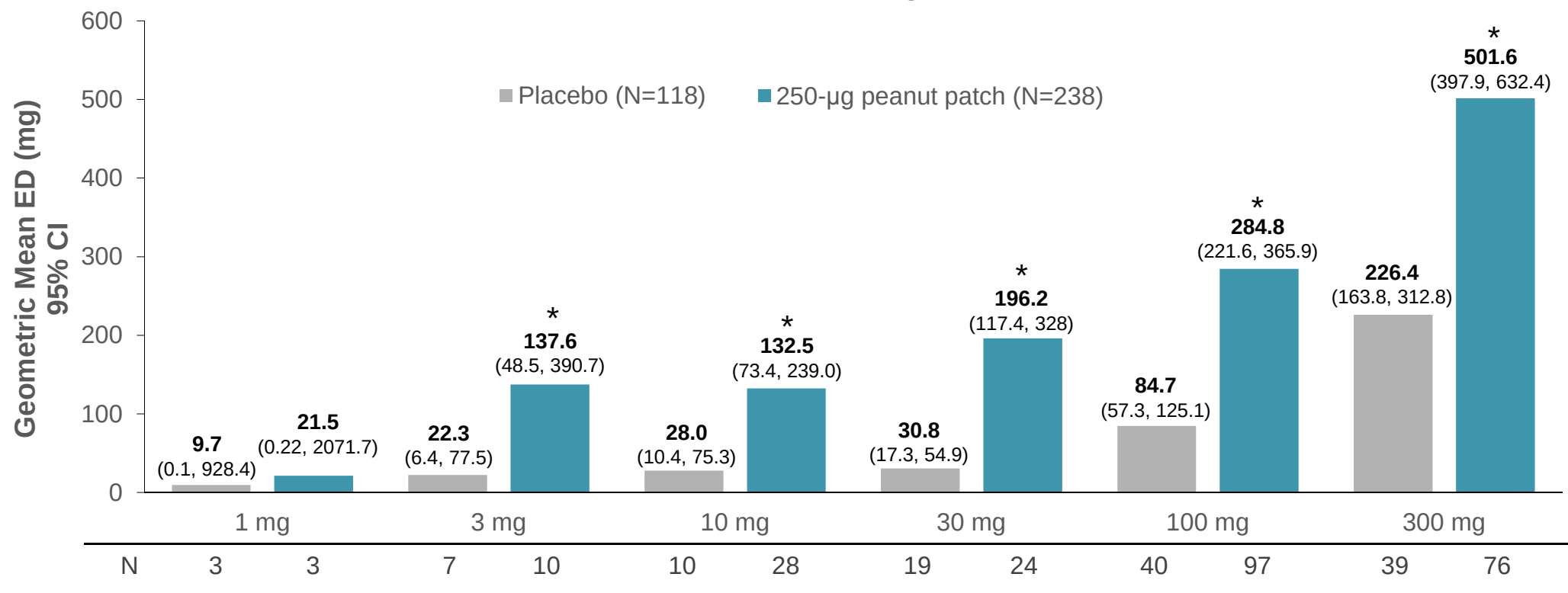


Figure 2

