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EDITORIAL

Low dose immunotherapy in very young children to treat peanut allergy

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Peanut allergy is a serious, typically life-long, and potentially fatal immunologic condition growing in prevalence, now affecting approximately 1% of individuals in the U.S. and other developed nations [1]. A recent landmark prevention study called Learning Early About Peanut Allergy (LEAP) demonstrated an impressive 80% relative reduction in peanut allergy at age 5 among high-risk children randomized to early oral consumption of peanut compared to those continuing avoidance [2]. However, strict avoidance of peanut is critical for the estimated 3 million already living with peanut allergy, because there is no approved interventional treatment. As a result, patients and their caregivers must be constantly ready to recognize and treat anaphylaxis with autoinjectable epinephrine given that exposure to even traces of peanut protein can trigger anaphylaxis, a rapid and unpredictable systemic hypersensitivity reaction that can be life-threatening [3]. Indeed, allergies to tree nuts and peanuts are the leading cause of food allergy deaths, which disproportionately affect adolescents and young adults [4]. Food allergies in general are the commonest causes of outpatient anaphylaxis and causes over 200,000 annual emergency visits [5]. An ever-present and unpredictable threat of life-threatening anaphylaxis profoundly reduces health-related quality of life, greater than other common chronic childhood diseases like type 1 diabetes [6]. Clearly an effective disease-modifying therapy remains an urgent unmet need with public health implications.

Allergen immunotherapy is a highly effective antigen-specific, disease-modifying treatment and has been repeatedly shown to prevent or attenuate other forms of potentially life-threatening anaphylaxis (e.g. stinging insect hypersensitivity). There has been much recent investigation into developing food immunotherapy through various routes of administration – oral, sublingual, and epicutaneous. Of these, oral immunotherapy (OIT) is unique in its documented 100+ year history in the medical literature. Four recent randomized, controlled trials [7–10] have provided convincing evidence that daily peanut OIT can induce immunomodulation that results in a significant reduction in clinical reactivity. This reduction of clinical reactivity is called desensitization and is generally believed to be transient, requiring ongoing regular therapy to maintain. However, while desensitization remains a potentially life-changing advance for peanut-allergic individuals, a

more permanent change (e.g. ‘sustained unresponsiveness (SU)’ or ‘clinical tolerance’) that would allow discontinuation of therapy and reintroduction of the previously allergenic food remains a key research goal.

To address this goal, our research group, led by Dr. Wesley Burks, hypothesized that early intervention OIT (E-OIT) initiated in preschool children would improve long-term outcomes. This hypothesis was based on three clinical observations. First, in our pilot studies, a lower peanut-specific IgE (psIgE) level at baseline was significantly associated with improved clinical outcomes following OIT [11]. Second, longitudinal studies have shown that psIgE tends to be lowest in early life, only to characteristically intensify in the preschool years in persistent peanut allergy [12], a process that may be IL-4 driven [13] and predictive of life-long allergy by age 2 [14]. Finally, several recent studies suggest that IgE responses are common in infants and may emerge prior to terminal differentiation of the pro-allergic CD4⁺ T_H2 T cell population. For example, almost 70% of 512 high-risk American infants were sensitized to peanut prior to known exposure, with 27% already having high titer psIgE [15]. Yet in such infants, T cell receptor affinity is often weak and the expression of the canonical T_H2 transcription factor GATA-3 is unstable. Taken together, these data suggest the existence, during the preschool years, of a critical window of developmental plasticity in early allergic programming, which will consolidate if not interrupted. We consider this theoretical window the optimal opportunity for therapeutic intervention in peanut allergy.

To test our hypothesis, we designed and performed a randomized clinical trial of low- and high-dose E-OIT, targeting young children aged 9–36 months with any positive skin test or detectable psIgE who were already known to be clinically allergic to peanut, or those who had high-grade sensitization (i.e. psIgE >5 kU_A/L) but who were not yet orally exposed. This was, to our knowledge, the first trial to specifically target this preschool age group for OIT treatment. Our early intervention aim required enrollment within 6 months of the index reaction for known allergic patients. The diagnosis of peanut allergy was confirmed in all subjects with an oral peanut challenge at baseline, and subjects were then block-randomized 1:1 to receive low-dose (target maintenance dose, 300 mg/day peanut protein) or high-dose (3000 mg/day peanut protein) E-OIT.

Further details about the protocol can be explored elsewhere [16]. The primary end point was the proportion of subjects in the intent-to-treat population achieving SU at 4 weeks after discontinuing E-OIT, defined as the ability to consume 5 g of peanut protein (the equivalent of about 20 peanuts) without dose-limiting symptoms during an exit food challenge, followed by one additional serving size of peanut. Primarily due to safety and feasibility concerns, we did not feel that it would be possible for the first study of OIT in peanut-allergic infants and toddlers to include a placebo control. We therefore chose a prespecified comparator of a matched control group undergoing standard-care peanut avoidance at the pediatric allergy center at Johns Hopkins, which has a very similar clinic population to our own and is very experienced in longitudinal studies of peanut and other food allergies [17]. As our aim was to establish 'clinical tolerance' permitting free consumption of peanut in the diet after stopping therapy, we powered the study *a priori* for a comparison of the frequency of peanut consumption in the diet following OIT or standard allergen avoidance.

Overall, 29/37 (78%) of the intent-to-treat population achieved the primary end point over a median of just 29 months, whereas it was 29/32 (91%) overall in those completing the protocol, the highest rates of 4-week SU yet reported in the literature. E-OIT was immunomodulatory, associated with significant mast cell suppression and the contraction and expansion from baseline of pslgE and IgG4 levels, respectively, in all E-OIT-treated children, with no significant differences between the low- and high-dose arms in immunologic or clinical end points. At the end of the observation period, children receiving E-OIT were 19 times more likely to be able to successfully consume dietary peanut than matched standard-care controls, in whom pslgE significantly increased. Consistent with data from other OIT studies, adverse events (AEs) were common but all were graded as mild or moderate; there were no SAEs during the trial and no AEs that were graded severe. One patient required a single dose of epinephrine for a related AE at home. As reported previously, and consistent with oral allergen exposure, AEs related to the gastrointestinal tract were the most common classification of observed AEs observed and led to treatment discontinuation in 3/37 (8%) of subjects.

While there are some clear limitations to the study, chief among them the lack of a randomized placebo control, we believe this pilot trial of E-OIT contributes several key findings. First, OIT in peanut-allergic infants and toddlers is feasible and has an acceptable safety profile that is as good as, if not better, than previously reported in other OIT trials. Secondly, almost 80% of the randomized study population was able to successfully introduce peanut-containing foods into the diet *ad libitum* 4 weeks after stopping treatment. Notably, this occurred at 1/13th the maintenance dose and in approximately half of the time when compared to older children in the only other peanut OIT study to report on 4-week SU [11]. In part because we cannot be certain that these children have achieved permanent tolerance, we are continuing to follow them in a long-term observational follow-up study conducted by our group to better assess their long-term clinical

outcomes. However, we believe that the very low rate of spontaneous tolerance observed in controls strongly suggests that E-OIT has the potential to be an effective disease-modifying therapy, especially when started soon after the initial presentation, when pslgE levels tend to be the lowest. Thirdly, while underpowered for a direct head-to-head comparison, there appeared to be no difference between 300 and 3000 mg/day in terms of clinical efficacy and immunoregulation, suggesting that low-dose therapy is highly effective in young children and that higher doses provide no clear additional benefit.

Taken together, these findings support our hypothesis that E-OIT effectively disrupts peanut allergy and enhances outcomes, perhaps due to the plasticity of a relatively recently primed T_H2 program. The existence of such plasticity, and its manipulation by oral exposure, was supported by the LEAP study and its extension study LEAP-ON [18], in which high-risk infants who had not yet developed peanut allergy were tolerized by regular oral peanut exposure. In our E-OIT trial, we recruited a slightly older population who already had confirmed peanut allergy, and we showed that even after immediate hypersensitivity is clinically evident, allergic programming to peanut may still be effectively disrupted through regular oral exposure. We eagerly await data from other similar controlled studies, and from the long-term follow-up of this trial. If those data are positive, we believe that E-OIT has transformative potential for the future treatment of peanut allergy. We can envision a future standard of care in which infants and young children are assessed early for their place on a peanut allergy continuum. For those eligible, the LEAP-based interventions should prove valuable to prevent peanut allergy at scale, whereas for those already affected, E-OIT could be used as a hand-in-hand public health strategy to offer a safe and highly effective rescue treatment.

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Declaration of interest

B Vickery is an employee of Aimmune Therapeutics. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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