

Correspondence and Replies

Intense allergic reactions to personalized oral immunotherapy treatments for food allergies at home



To the Editor:

We examined the study by Nachshon et al,¹ which analyzed the rate and risk factors for allergic reactions, specifically anaphylaxis, in patients treated at home with food allergy (FA) oral immunotherapy (OIT). To further enhance the quality of this study, it might be beneficial to take into account the following suggestions.

First, Nachshon et al¹ conducted their study with a predetermined minimal maintenance dose to achieve desensitization via OIT, and for some participants, potentially free consumption of the allergens without anaphylaxis. This study did not specify the basis for determining the threshold dosage for free consumption. It is essential to personalize both the minimal maintenance dose and the threshold dosage for each participant. This is underscored by Mori et al's study, which suggests that individual antigen tolerance is key for optimal patient outcomes. Applying a universal minimal maintenance dose may pose a risk, especially for those with heightened IgE binding to allergens.² In subsequent research, it might be beneficial to gauge each participant's minimal maintenance dose through IgE binding tests, ensuring a treatment plan suited to their immune responses.²

Second, this study spanning from April 2010 to January 2020 includes some variability in the approach to data collection over this period. In the initial 2 years, data were obtained through free-text email feedback from patients. However, in the 8 years that followed, a more structured electronic web-reporting system was employed. Such variation in data collection techniques could potentially result in discrepancies in how patient feedback is understood by researchers. It is also important for the authors to acknowledge that there is no universally accepted grading system for acute allergic reactions, even though they used structured questions grounded in the Delphi study grading system.³

Third, both total IgE and specific IgE are of paramount significance in allergic diseases.⁴ Introducing quantitative IgE metrics to the HETR (high-grade home epinephrine-treated reaction) assessment framework would mitigate potential confounders, such as coexisting medical conditions that could influence SpO₂, blood pressure, and central nervous system activity, thus refining the accuracy of HETR categorization.⁵ It is also pertinent to note that there is an observed escalation in IgE levels during the course of oral immunotherapy, preceding either full or partial desensitization, which can precipitate augmented or unpredictable allergic reactions.⁶

In summary, the study by Nachshon et al¹ reveals major risk factors that individuals and their physicians should consider before OIT treatment at home and indicates the necessary steps to desensitize patients. To improve this study, we suggest further

elaboration on free consumption desensitization thresholds identified in this study, consistent analysis of data received in a structured format from the web-reporting system, and additional quantitative data via IgE blood testing.

Jarrod Van Loon, BS^a

Patrick Wu, BS^a

Su-Boon Yong, MD, PhD^{b,c}

^aCollege of Medicine, Lake Erie College of Osteopathic Medicine, Bradenton, Fla

^bDepartment of Allergy and Immunology, China Medical University Children's Hospital, Taichung, Taiwan

^cDepartment of Medicine, College of Medicine, China Medical University, Taichung, Taiwan.

No funding was received for this work.

Conflicts of interest: The authors declare that they have no relevant conflicts of interest. Received for publication September 27, 2023; accepted for publication November 7, 2023.

Corresponding author: Su-Boon Yong, MD, PhD, Department of Allergy and Immunology, China Medical University Children's Hospital, No. 2, Yuh-Der Rd, Taichung City 404, Taiwan. E-mail: yongsuboon@gmail.com.

REFERENCES

1. Nachshon L, Schwartz N, Levy MB, Goldberg M, Epstein-Rigbi N, Katz Y, et al. Severe anaphylactic reactions to home doses of oral immunotherapy for food allergy. *J Allergy Clin Immunol Pract* 2023;11:2524-33.e3.
2. Mori F, Barni S, Liccioli G, Novembre E. Oral immunotherapy (OIT): a personalized medicine. *Medicina (Kaunas)* 2019;55:684.
3. Dribin TE, Schnadower D, Spergel JM, Campbell RL, Shaker M, Neuman MI, et al. Severity grading system for acute allergic reactions: a multidisciplinary Delphi study. *J Allergy Clin Immunol* 2021;148:173-81.
4. Yue D, Ciccolini A, Avilla E, Wasserman S. Food allergy and anaphylaxis. *J Asthma Allergy* 2018;11:111-20.
5. Liang Y, Ganley-Leal LM. A simple method for measuring human cell-bound IgE levels in whole blood. *J Immunol Methods* 2009;343:134-9.
6. Akarsu A, Brindisi G, Fiocchi A, Zicari AM, Arasi S. Oral immunotherapy in food allergy: a critical pediatric perspective. *Front Pediatr* 2022;10:842196.

<https://doi.org/10.1016/j.jaip.2023.11.015>

Reply to "Intense allergic reactions to personalized oral immunotherapy treatments for food allergies at home"



To the Editor:

In their correspondence to our article "Severe anaphylactic reactions to home doses during oral immunotherapy for food allergy,"¹ Van Loon et al² made several comments. First, they suggest to determine a minimal maintenance dose for each patient using IgE binding to allergens. We would first like to emphasize that our study was not a clinical trial but rather a retrospective analysis of the course and outcome of a real-world clinical oral immunotherapy (OIT) treatment program for multiple foods.³⁻⁷ Second, the minimal maintenance dose in our OIT program is aimed to be a dose that would significantly reduce the risk for reactions on accidental exposure based on previous publications.^{8,9} Most severe home anaphylactic reactions in our patients were

experienced before this protective dose was reached, and we do not see a rationale in providing maintenance doses that would be too low to confer sufficient protection. As for IgE binding, this is not a clinically available test in most countries.

The second comment by Van Loon et al relates to potential reporting bias given different reporting methods on home reactions during the study period. An accurate and timely electronic report of the home treatment phase was required since the OIT program started in April 2010. Indeed, as detailed in the article, between 2010 and 2012, the reports were provided via email, whereas in later years we transitioned to a web-reporting system, which was based on a structured questionnaire and provided better information regarding each reaction.¹⁰ However, this study focuses on reactions experienced by the patients as severe and treated with epinephrine. Such reactions cannot be overlooked or underreported by patients. They are alarming, requiring medical care, and necessitating treatment modifications. Therefore, such reactions were universally reported from the beginning of our OIT treatment program regardless of the reporting method. Data collected on each reaction included organ systems involved and treatment provided, and high-grade home epinephrine-treated reactions (HG-HETRs) were defined based on objective criteria, including vital sign impairment. Therefore, we do not see how the lack of a universally accepted grading system would affect our results.

The third comment by Van Loon et al suggests that using total and specific IgE (sIgE) levels could refine the accuracy of HG-HETR categorization and that the known phenomenon of the initial increase in sIgE during OIT might predict such reactions. As to the first point, sIgE was shown in several studies to predict adverse reactions during OIT.¹¹ As sIgE is not routinely used in Israel, the skin prick test (SPT) wheal size is a valid alternative and performs even better for certain foods (eg, sesame and tree nuts). We have previously shown that although SPT was a predictor of HETR on univariate analysis, significance was lost on multivariate analysis.¹² SPT was not predictive of HG-HETR in the current study. The large population studied (1637 patients), which is essential for characterization of a phenomenon with low incidence (only 1.65%) to be accurate, is far larger than any previous study. Therefore, although we cannot predict how sIgE would perform in this case, it seems unlikely that it would perform better than SPT. Total IgE has no role, neither in the diagnosis of food allergy nor in assessing its severity. The increase in sIgE during the first months of OIT is a known phenomenon. The immune system undergoes several modifications during the process of desensitization, affecting IgG4 production, basophil reactivity, T-cell subtypes, and additional aspects. We are not aware of any study showing that the initial increase in sIgE during OIT is a predictor or that it is even associated with increased risk of reactions. In addition, as this phenomenon occurs during the initial stages of OIT, it cannot be used as a pretreatment marker to predict adverse reactions.

The ability to identify patients at risk for HG-HETRs before the beginning of OIT is highly important¹³ as it can

be used to recommend alternative treatments, that is, biologicals.

Liat Nachshon, MD^{a,b}
Naama Schwartz, PhD^c
Michael B. Levy, MD^d
Michael Goldberg, MD, PhD^{a,d}
Naama Epstein-Rigbi, MD^{a,d}
Yitzhak Katz, MD^{a,d}
Arnon Elizur, MD^{a,d}

^aYitzhak Shamir Medical Center, Institute of Allergy, Immunology and Pediatric Pulmonology, Zerifin, Israel

^bDepartment of Medicine, Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

^cSchool of Public Health, University of Haifa, Haifa, Israel

^dDepartment of Pediatrics, Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel. M. Goldberg is funded by a Kamea grant from the Ministry of Health, Israel, and Y. Katz is supported by the Leon Alcalay Chair in Pediatric Immunology, Tel Aviv University. Conflicts of interest: The authors declare that they have no relevant conflicts of interest.

Received for publication November 3, 2023; accepted for publication November 7, 2023.

Corresponding author: Liat Nachshon, MD, Yitzhak Shamir Medical Center, Institute of Allergy, Immunology and Pediatric Pulmonology, Bldg 131, Beer Yaakov, Zerifin 70300, Israel. E-mail: Liatna2@gmail.com.

REFERENCES

- Nachshon L, Schwartz N, Levy MB, Goldberg MR, Epstein-Rigbi N, Katz Y, et al. Severe anaphylactic reactions to home doses during oral immunotherapy for food allergy. *J Allergy Clin Immunol Pract* 2023;11:2524-33.
- Van Loon JJ, Wu P, Yong SB. Intense allergic reactions to personalized oral immunotherapy treatments for food allergies at home. *J Allergy Clin Immunol Pract* 2024;12:797.
- Levy MB, Elizur A, Goldberg M, Nachshon L, Katz Y. Clinical predictors for favorable outcomes in an oral immunotherapy program for IgE-mediated cow's milk allergy. *Ann Allergy Asthma Immunol* 2014;112:58-63.e1.
- Nachshon L, Goldberg MR, Katz Y, Levy MB, Elizur A. Long-term outcome of peanut oral immunotherapy—real life experience. *Pediatr Allergy Immunol* 2018;29:519-26.
- Nachshon L, Goldberg MR, Levy MB, Appel MY, Epstein-Rigbi N, Lidholm J, et al. Efficacy and safety of sesame oral immunotherapy—a real-world, single-center study. *J Allergy Clin Immunol Pract* 2019;7:2775-81.e2.
- Elizur A, Appel MY, Nachshon L, Levy MB, Epstein-Rigbi N, Pontoppidan B, et al. Walnut oral immunotherapy for desensitizing of walnut and additional tree nut allergies (Nut CRACKER): a single-centre, prospective cohort study. *Lancet Child Adolesc Health* 2019;3:312-21.
- Elizur A, Appel MY, Nachshon L, Levy MB, Epstein-Rigbi N, Koren Y, et al. Cashew oral immunotherapy for desensitizing cashew-pistachio allergy (NUT CRACKER study). *Allergy* 2022;77:1863-72.
- Baumert JL, Taylor SL, Koppelman SJ. Quantitative assessment of the safety benefits associated with increasing clinical peanut thresholds through immunotherapy. *J Allergy Clin Immunol Pract* 2018;6:457-65.
- Levy MB, Goldberg MR, Nachshon L, Tabachnik E, Katz Y. Lessons from cases of mortality due to food allergy in Israel: cow's milk protein should be considered a potentially fatal allergen. *Isr Med Assoc J* 2012;14:29-33.
- Nachshon L, Goldberg MR, Elizur A, Levy MB, Schwartz N, Katz Y. A web site-based reporting system for monitoring home treatment during oral immunotherapy for food allergy. *Ann Allergy Asthma Immunol* 2015;114:510-5.
- Patel N, Vazquez-Ortiz M, Turner PJ. Risk factors for adverse reactions during OIT. *Curr Treat Options Allergy* 2019;6:164-74.
- Nachshon L, Schwartz N, Tsvib L, Levy MB, Goldberg MR, Epstein-Rigbi N, et al. Patient characteristics and risk factors for home epinephrine-treated reactions during oral immunotherapy for food allergy. *J Allergy Clin Immunol Pract* 2021;9:185-92.e3.
- Allergic Living. Girl with milk allergy dies of severe reaction related to desensitization; 2021. Accessed January 18, 2023. <https://www.allergicliving.com/2021/12/20/girl-with-milk-allergy-dies-of-severe-reaction-related-to-desensitization>

<https://doi.org/10.1016/j.jaip.2023.11.014>