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RESPONSE TO THE LETTER TO THE EDITOR

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Peach sublingual immunotherapy for lipid transfer protein syndrome

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We thank Dr. Özdemir for his interest in our article and for his thoughtful comments regarding our study on peach sublingual immunotherapy (Pru p3 SLIT) in patients with lipid transfer protein (LTP) syndrome. We appreciate the opportunity to clarify several methodological aspects of our study.

First, regarding the terms—remission, resolve, and improve—our intention was to distinguish between two different clinical scenarios. In our study, clinical remission refers to the ability of patients to tolerate previously implicated plant foods after treatment, as confirmed by oral food challenges and subsequent dietary reintroduction. However, in patients with cofactor-associated reactions, tolerance was achieved only in the absence of cofactor. These patients tolerated the food itself after treatment but also developed clinical manifestations if the food was consumed in combination with the triggering cofactor. For this reason, we concluded that while Pru p3 SLIT may induce remission of food allergy, it does not prevent reactions triggered by cofactors. Importantly, this distinction may have relevant clinical implications, as cofactors may not always be recognized during diagnostic evaluation and could partially explain the apparent lack of response to Pru p3 SLIT observed in some patients.

Second, the identification of cofactors, such as exercise or non-steroidal anti-inflammatory drugs (NSAIDs), was based on a detailed clinical history obtained during routine allergological evaluation. In routine clinical practice, controlled provocation tests with exercise or NSAIDs are rarely performed because of safety concerns. Therefore, as in most published studies on LTP syndrome, the involvement of cofactors was determined from the patient's clinical history. Only one patient reported reactions associated with the intake of NSAID, and the specific drug was not recorded systematically.

Regarding the treatment protocol, the study was conducted in a real-life clinical setting over several years. In routine practice, Pru p3 SLIT is usually maintained for 3-5 years, with duration individualized according to clinical response and judgment of physician, which may explain differences across studies. In our cohort, the mean treatment duration (3.4 years) reflected the overall follow-up, whereas the meantime to the first oral food challenge (2.7 years) matched the time of tolerance assessment. As stated

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in the manuscript, a standardized protocol was implemented in 2022, including oral challenges with unpeeled peach after 1 year of treatment. Because most data were collected prior to this protocol, the timing and sequence of food challenges were based on each allergist's clinical judgment. In the study, challenges were performed in a stepwise manner, starting with peach and followed by other implicated foods depending on the response.

Regarding safety, our results confirmed the favorable safety profile of Pru p3 SLIT, with no adverse reactions in most patients and only mild events observed and described clearly (only one local [oral itchy] and another mild grade 2 systemic reaction [itchy lips and a few facial wheals]).

We acknowledge that the description of the study population could have been clearer. Of the initial 80 patients diagnosed with LTP syndrome, 49 started Pru p3 SLIT. However, to assess effectiveness of treatment, it was necessary to have results from oral food challenges with unpeeled peach performed after at least 1 year of treatment. This criterion was fulfilled by 23 patients, and therefore the analysis was focused on this subgroup. The demographic data reported in the Results section matched these 23 patients who completed the evaluation protocol. Figure 2 summarized the patients' election process and follow-up. Prior to the implementation of our standardized protocol, differences in clinical management and follow-up could have explained some of the variability observed in the number of patients at each stage.

The proportion of 95.7% refers to the patients who tolerated oral challenge with unpeeled peach after treatment. The subgroup of seven patients with cofactor-associated reactions represented a specific clinical phenotype within the cohort. These patients tolerated the food in isolation but not when the cofactor was present; therefore, this proportion described different clinical outcomes rather than additive proportions. This finding further supported the concept that cofactor-dependent reactions involved mechanisms beyond allergen exposure alone. Finally, we agree that the evaluation of immunological markers, such as specific immunoglobulin E (IgE) or immunoglobulin G4 (IgG4) to Prup 3 could provide additional information on the mechanisms underlying tolerance induction. However, because this was a retrospective real-life study, these parameters were not measured systematically, which we acknowledge as a limitation.

We thank Dr. Özdemir for his comments, which allowed us to clarify these aspects of our study and further underlined the clinical relevance of distinguishing between classic LTP food allergy and cofactor-dependent reactions.

Mandatory Disclosure on Use of Artificial Intelligence

The authors declare that no AI-assisted tools were used in the preparation of this manuscript. All references have been manually verified for accuracy and relevance.