LETTER TO THE EDITOR

Long-term clinical and immunological evolution of patients with LTP syndrome: real-life study

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To the Editor,

Lipid Transfer Proteins (LTPs) are major plant food allergens, particularly prevalent in Rosaceae fruits but also present in other plant foods, such as nuts, and even in pollens (1) (2).

Sensitization to LTPs can lead to clinical reactions ranging from mild oral allergy syndrome (OAS) to systemic responses including anaphylaxis. Cross-reactivity among LTPs can result in progressively broader food allergies, a condition referred to as LTP Syndrome (1) (3) (4).

Betancor D *et al* reported that 1/3 of 113 patients with 10 years of LTP food allergy developed allergy to new foods (5) and, 1/10 of patients sensitized to LTPs developed allergies to plant foods (5). Similarly, Asero *et al*, reported that throughout one year after diagnosis of LTP Syndrome, 67 (27%) patients developed allergies to other plant foods (6). In clinical practice, optimal management of LTP Syndrome involves patient education on the avoidance of causative foods but also prompt recognition and appropriate treatment of unpredictable acute reactions. Allergen-specific immunotherapy is currently the only treatment with a potential to modify the natural course of allergic diseases in the long-term (7) (8). Since 2011, Sublingual Immunotherapy (SLIT) with Pru p 3 has been used in patients with LTP Syndrome and peach allergy, for the acquisition of tolerance to this allergen in several countries, including Portugal (7) (8) (9).

On a short-term evaluation, sublingual Immunotherapy (SLIT) with Pru p 3 has been shown to be effective and safe in LTP syndrome (4)(9), with desensitization rates of 72–100% upon one year treatment (10). However,

there is still very limited data on its long-term impact on tolerance acquisition and prevention of new sensitizations. We aimed to report long-term clinical and immunologic evolution of a cohort of patients with LTP syndrome and explore the potential lasting effects of Pru p 3 sublingual immunotherapy (SLIT Pru p 3). This retrospective real-life study included 22 patients followed for LTP syndrome at a tertiary hospital Immunoalergology Department (average follow-up 10±1 years). A subgroup underwent treatment with SLIT Pru p 3 for a minimum of 1 year. Demographic, clinical, and immunological data were collected from medical records. Clinical evolution was analyzed comparing clinical manifestations at diagnosis (T0) and within 2 years prior to the last follow-up (T1), minimum 8 years after diagnosis. Tolerance to previously offending foods, and reactions to new foods reported were also recorded at T1. Food sensitization was assessed, at T0 and T1, by skin prick tests (SPT) performed during clinical evaluation, using extracts from fruits, nuts, seeds, and purified molecular allergen Pru p 3. Specific IgE/total serum IgE ratios for peach and Pru p 3, and molecular profiles using a IgE multiplex assay (ISAC-Thermo Fisher Scientific) were also determined at T0 and T1. Statistical analysis was conducted using SPSS v21.0. Most patients had allergic rhinitis (26%), and 23% had asthma.
At diagnosis (T0), anaphylaxis was the most common reaction (54%), followed by urticaria (32%), angioedema (9%), and OAS (4%). Main triggers were Rosaceae fruits (96%), especially peach (82%). Tree nuts and peanuts were other offending foods frequently reported, (50% and 32% respectively).

Notably, at the last follow-up evaluation (T1), urticaria and OAS became the most frequent clinical manifestations (both 36%). No patients reported anaphylaxis within 2 years prior to follow-up (T1), likely from continued /educated food avoidance. Most patients continued to avoid at least one high-risk food. Of note, at T1 13/22 patients (59%) tolerated previously offending foods, while 6/22 (27%) reported reactions to new foods: tomato (n=2), sesame/sunflower seeds (n=2), almond (n=2), plum (n=1), grapes (n=1), peanuts (n=1), and kiwi (n=1).

The mean peach-specific IgE/total serum IgE ratio significantly decreased from T0 and T1 (0.13±0.16 to 0.08±0.1, p=0.01), although Pru p 3-specific IgE/total serum IgE did not decrease significantly. In our cohort, the molecular profile, assessed by IgE multiplex assay, revealed that, throughout follow-up, the frequency of patients sensitized to more than 5 LTPs changed from 31% at T0 to 37% at T1, without reaching statistical significance ($p>0.05$). These results indicate that, in our sample, the molecular profiles observed were overall similar across the study, contrast with previous reports that suggested a progression to a broader sensitization profile throughout follow-up of LTP syndrome (5) (6) (11). We observed a non-significant increase in sensitizations to Par j 2 and Jug r 3 (3 vs 5 and 13 vs 16, respectively). While the increase in sensitization to Jug r 3 may indicate a potential trend toward greater risk of severity over time, and co-sensitization to Par j 2 might exert a protective effect (12) (13), these observations remain speculative and cannot be conclusively interpreted and generalized from our study, partly due to its small sample size.

Thirteen patients underwent SLIT with Pru p 3 for mean 2.5±1.4 years. All patients included had stopped SLIT minimum 7 years before T1 to allow evaluation of its long-term impact. Notably, no significant differences in demography or clinical manifestations were found at T0 between SLIT and non-SLIT groups (Table I).

Importantly, although numerical differences were noted between SLIT and non-SLIT groups regarding severity of clinical manifestations at T0 (anaphylaxis 8 vs 4, urticaria 4 vs 3, angioedema 1 *vs* 1, and OAS 0 *vs* 1) and at T1 (urticaria 5 *vs* 3, angioedema 0 *vs* 2, and OAS 4 *vs* 4), these disparities did not attain statistical significance, possibly reflecting the small sample size.

Upon follow-up, at T1, both tolerance acquisition to previously offending foods and reactions to new foods were both more common in SLIT patients compared to non-SLIT (69% *vs* 44% and 31 *vs* 22% respectively), however without statistical significancy. Regarding evolution of sensitization profile, no differences in the frequencies of positive SPT were found, between SLIT and non-SLIT group, at both T0 and T1 (Figure 1a), or in IgE multiplex assay profiles (Figure 1b). The percentage of patients sensitized to more than five LTP components remained stable in the SLIT group (40%) but increased in the non-SLIT group (22% to 33%), although not significantly. Importantly, the SLIT group showed a significant reduction in peach-specific IgE/total serum IgE ratio from T0 to T1 [0.04(0.2) *vs* 0.03(0.14), p=0.02], with no significant changes observed in Pru p 3-specific IgE/total serum IgE ratios in either group (Figure 1c).

The duration of SLIT Pru p 3 treatment varied among the 13 patients and was often less than 3 years, which limits the conclusions that can be drawn regarding SLIT effectiveness. Interestingly, at T1 evaluation, frequency of SLIT patients reporting tolerance to previously offending foods where higher when compared with non-SLIT patients (69% *vs* 44%), although this difference was not significant. In parallel, reactions to new foods were reported at T1, by both SLIT (31%) and non-SLIT patients (22 %).

We acknowledge retrospective design, limited sample size, clinical heterogeneity, and ongoing food avoidance as factors that may constrain the interpretation and generalizability of our study. Larger population and long-term prospective studies are needed to assess LTP syndrome clinical and immunological evolution, and the putative role of SLIT Pru p 3.

The significant decrease observed in peach-specific IgE/total serum IgE in SLIT patients, may indicate an immunological shift, reinforcing the interest on SLIT Pru p 3 as a therapeutic intervention (8) (14).

Our report on long-term follow-up of a food allergy cohort also shows that accurate diagnosis and patient education reduce incidence of severe reactions over time. Follow-up protocols and individualized allergy assessments are key to avoiding unnecessary dietary restrictions and improve patient´s confidence.

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Contributions

AB, SLS, CC: conceptualization, formal analysis, writing – original draft, writing – review & editing. AB, DS, SLS, CC: methodology, data curation

Conflict of Interest

The authors also declare that there is no existence of economic or other types of conflicts of interest regarding the presented article.

Protection of Human and Animal Subjects

The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and those of the Code of Ethics of the World Medical Association (Declaration of Helsinki as revised in 2013).

References

1. Pascal M, Munõz-Cano R, Reina Z, Palacín A, Vilella R, Picado C et al. Lipid transfer protein syndrome: clinical pattern, cofactor effect and profile of molecular sensitization to plant-foods and pollens. Clin Exp Allergy. 2012 Oct;42(10):1529-39. doi: 10.1111/j.1365-2222.2012.04071.x.

2. Oeo-Santos C, Navas A, Benedé S, Ruíz-León B, Díaz-Perales A, Vogel L et al. New insights into the sensitization to nonspecific lipid transfer proteins from pollen and food: New role of allergen Ole e 7. Allergy. 2020 Apr;75(4):798-807. doi: 10.1111/all.14086.

3. Gomez F, Bogas G, Gonzalez M, Campo P, Salas M, Diaz-Perales A et al. The clinical and immunological effects of Pru p 3 sublingual immunotherapy on peach and peanut allergy in patients with systemic reactions. Clin Exp Allergy. 2017 Mar;47(3):339-350. doi: 10.1111/cea.12901. PMID: 28160513.

4. González Pérez A, Escudero Pastor AI, Sola Martínez RA, Carbonell Martínez A. Evolution of laboratory parameters in patients with lipid transfer protein syndrome after 3 years of immunotherapy. Allergol Immunopathol (Madr). 2023 May 1;51(3):80-84. doi: 10.15586/aei.v51i3.790.

5. Betancor D, Gomez-Lopez A, Villalobos-Vilda C, Nuñez-Borque E, Fernández-Bravo S, De Las Heras Gozalo M et al. LTP Allergy Follow-Up Study: Development of Allergy to New Plant Foods 10 Years Later. Nutrients. 2021 Jun 24;13(7):2165. doi: 10.3390/nu13072165.

6. Asero R, Piantanida M, Pravettoni V. Allergy to LTP: to eat or not to eat sensitizing foods? A follow-up study. Eur Ann Allergy Clin Immunol. 2018 Jul;50(4):156-162. doi: 10.23822/EurAnnACI.1764-1489.57.

7. Pajno GB, Fernandez-Rivas M, Arasi S, Roberts G, Akdis CA, Alvaro-Lozano M. EAACI Allergen Immunotherapy Guidelines Group. EAACI Guidelines on allergen immunotherapy: IgE-mediated food allergy. Allergy. 2018 Apr;73(4):799-815. doi: 10.1111/all.13319.

8. Schoos AM, Bullens D, Chawes BL, Costa J, De Vlieger L, DunnGalvin A et al. Immunological Outcomes of Allergen-Specific Immunotherapy in Food Allergy. Front Immunol. 2020 Nov 3;11:568598. doi: 10.3389/fimmu.2020.568598.

9. Costa C, Duarte F, Pedro E, Melo AC, Barbosa MP, Santos MC. Imunoterapia sublingual com pêssego (Pru p 3) – Eficácia e segurança. Rev Port Imunoalergologia 2015; 23 (4): 211-222.

10. Rossi CM, Lenti MV, Merli S, Licari A, Marseglia GL, Di Sabatino A. Immunotherapy with Pru p 3 for food allergy to peach and non-specific lipid transfer protein: a systematic review. Clin Mol Allergy. 2023 May 31;21(1):3. doi: 10.1186/s12948-023-00184-5.

11. Asero R, Mistrello G, Roncarolo D, Amato S. *Relationship between peach lipid transfer protein specific IgE levels and hypersensitivity to non-Rosaceae vegetable foods in patients allergic to lipid transfer protein.* Ann Allergy Asthma Immunol. 2004 Feb;92(2):268-72. doi: 10.1016/S1081-1206(10)61559-1.

12. Paulino M, Costa C, Pedro E, Pereira-Santos MC. Molecular sensitization profile of patients with lipid transfer protein syndrome and associated clinical characteristics. Arq Asma Alerg Imunol. 2021;5(2):179-185.

13. Bogas G, Muñoz-Cano R, Mayorga C, Casas R, Bartra J, Pérez N et al. *Phenotyping peach-allergic patients sensitized to lipid transfer protein and analysing severity biomarkers.* Allergy. 2020 Dec;75(12):3228-3236. doi: 10.1111/all.14447. .

14. Sahiner UM, Giovannini M, Escribese MM, Paoletti G, Heffler E, Alvaro Lozano M. Mechanisms of Allergen Immunotherapy and Potential Biomarkers for Clinical Evaluation. J Pers Med. 2023 May 17;13(5):845. doi: 10.3390/jpm13050845.

Table I: Characterization of study population

	Total Patients(n=22)	SLIT (n=13)	Non-SLIT (n=9)	*p* value
Female, %	81.8	76.9	88.9	>0.05
Age (median±IQR, years)	39±9	40±9.1	37.4±8.8	>0.05
Age at the onset of symptoms (median±IQR, years)	20±10	17.3±9.7	22.8±10.9	>0.05
Follow-up time (mean±DP, years)	10±1	10.6±0.4	9.44±1.5	>0.05
Atopy, %	86.4	84.6	88.9	>0.05
Offending foods at baseline				
Rosacea fruits, %	95.5*	100	88.9	-
Nuts, %	50	53.8	44.4	>0.05
Peanuts, %	31.8	38.5	22.2	>0.05
Duration of SLIT Prup3 (mean±DP, years)	-	2.5±1.4	-	-
Time elapsed since end of SLIT (mean±DP, years)	-	9.1±1.6	-	-

* peach 81.8%

Figure 1: Immunological evolution upon follow-up (from diagnosis-T0 to T1) for SLIT and non-SLIT group. Frequency of positive skin prick tests (a); Number of positive LTP components in IgE multiplex assay (b); sIgE-peach/total IgE and sIgE-Pru p 3 /total IgE (c)