International Archives of Allergy and Immunology

Clinical Allergy – Research Article

Int Arch Allergy Immunol 2021;182:447–454
DOI: 10.1159/000512613

Received: April 9, 2020
Accepted: October 27, 2020
Published online: February 15, 2021

Pru p 3 Sublingual Immunotherapy in Patients with Lipid Transfer Protein Syndrome: Is It Worth?

Juan María Beitia[a, b] Arantza Vega Castro[a, b] Remedios Cárdenas[a, b] Maria Isabel Peña-Arellano[a, b]

[a]Allergy Service, Hospital Universitario de Guadalajara, Guadalajara, Spain; [b]ARADyAL Spanish Thematic Network and Co-operative Research Centre RD16/0006/0023, Spain

Keywords
Sublingual immunotherapy · Lipid transfer protein · Food allergy · Peanut allergy · Peach · Immunotherapy

Abstract
Background: Lipid transfer proteins (LTPs) syndrome is an important cause of multiple plant food allergy in the Mediterranean area. The effectiveness of sublingual immunotherapy (SLIT) with the LTP Pru p 3 extract has been little investigated in the real-world setting. This study aimed to investigate the outcome of Pru p 3 SLIT in real-life patients with LTP syndrome with/without concurrent reactions to peanut and/or nuts. ***Methods:*** This was a prospective real-life study including all patients diagnosed with LTP allergy and treated with Pru p 3 SLIT between 2011 and 2018 in a tertiary hospital in Spain. Patients underwent open oral food challenge (OFC) tests for unpeeled peach and nuts/peanuts 1 year after the treatment started to assess food tolerance. A control group of patients diagnosed with LTP allergy who refused treatment with immunotherapy were included. Severity of symptoms and diet avoidance was recorded in both groups. ***Results:*** Twenty-nine patients with a median age of 24.7 years (range 5.5–43.1) were included: 100% were allergic to fruit; 72%, to peanut and/or nuts; 19 had a history of severe systemic reactions. Seven patients discontinued therapy; 3 (10%), due to adverse events. One year after SLIT start, 16 (73%) patients had negative OFC to peach; 95%, after 2 years; 69% had negative OFC to nuts/peanuts. The control group included 13 patients: 53.8% experienced reactions with new foods; severity of symptoms increased significantly ($p < 0.001$), and diet restrictions were maintained in this group. ***Conclusions:*** SLIT with Pru p 3 shows a good safety profile, and avoid dietary restrictions in patients with LTP syndrome treated in the real-life setting.

Introduction

Plant food allergy is the most common food allergy in adults and adolescents, with *Rosaceae* fruits (e.g., peach, apricot, and apple) being the most frequent in

Juan M. Beitia and Arantza Vega Castro have equally contributed to the work and must, therefore, be both considered as first authors.
Edited by: H.-U. Simon, Bern.

karger@karger.com
www.karger.com/iaa

Arantza Vega Castro
Allergy Section, Hospital Universitario de Guadalajara
CL Donante de sangre s/n
ES–19002 Guadalajara (Spain)
avega@sescam.jccm.es

the Mediterranean area [1, 2]. The clinical presentation of plant food allergies includes a high incidence of anaphylactic reactions in which lipid transfer proteins (LTPs) are the main allergens involved in south Europe [3, 4].

LTPs are panallergens widely distributed among different plant species. They can be found in foods such as *Rosaceae* fruits, citrus fruits (e.g., oranges, and mandarins), nuts (e.g., peanuts, hazelnuts, and walnuts), or vegetables (e.g., tomatoes and lettuce) and are also present in several pollens [5, 6]. Of these, peaches are the most frequent cause of food allergy in the Mediterranean area, mainly due to LTP Pru p 3 [4, 7]. The high identity level between LTPs sequences, which ranges from 30 to 95% [8], along with their wide distribution among plant foods, makes LTP-sensitized patients at risk of reacting to multiple – and even non-taxonomically related – plant foods, leading to a set of clinical manifestations known as LTP syndrome [9].

The diagnosis of LTP syndrome is becoming increasingly frequent in routine clinical practice and results in a remarkable impact on patients' life. Avoiding exposure to the food responsible for allergic reactions is a mainstay in the management of these patients. The increasing frequency of these reactions entails important dietary restrictions, and more alarmingly, many patients eat these foods by accident, sometimes resulting in severe anaphylaxis. Owing to this risk, patients are often recommended to always carry epinephrine autoinjectors with them. Searching for an etiological treatment for LTP syndrome, various studies have proved the efficacy of sublingual immunotherapy (SLIT) with commercial allergenic extracts of Pru p 3 in increasing tolerance to peach in sensitized patients [10–12], even in those who had systemic reactions [12]. One of these studies showed that Pru p 3 SLIT desensitized not only to peach LTP but also to Ara h 9 in patients with concomitant allergy to peanuts [12]. However, studies assessing the effectiveness of Pru p 3 SLIT are still scarce, particularly in the setting of routine clinical practice, which often includes patients with a history of more severe systemic reactions than those enrolled in clinical trials. This study aimed to assess the effectiveness of Pru p 3 SLIT in patients diagnosed with LTP syndrome who had experienced allergic reactions in response to fruit and vegetable intake with/without concurrent reactions to nuts and/or peanuts, in all cases due to LTP allergy under routine clinical conditions, so reducing the severity of symptoms and avoiding the need of a restricted diet.

Methods

Study Design and Patients

This was a prospective and descriptive real-life study conducted in the Allergy Section of the University Hospital of Guadalajara, Spain. We designed a working protocol in 2011 to treat patients with allergy to LTP with Pru p 3 SLIT and to assess clinical effectiveness checking tolerance to the involved foods after 1 year of treatment and plant food avoidance at the end of the treatment. The period of analysis was from January 2011 to December 2018. The study protocol was approved by the local Ethics Committee.

The study included patients of any age diagnosed with LTP syndrome who agreed to start SLIT. Patients had to meet the following criteria: clinical history of an allergic reaction after eating several different fruits with/without symptoms with vegetables, and/or peanuts or nuts; positive specific IgE (sIgE) in skin and serological test to LTP; and serum levels of sIgE to rPru p 3 higher than other LTPs. We excluded patients diagnosed with allergy to other plant food proteins and patients who developed symptoms with LTP only in the presence of cofactors (exercise, NSAIDs intake, sleep deprivation, or asthma exacerbation). Patients allergic to LTP who refused to be treated with SLIT were included as a control group.

All patients had experienced at least 1 systemic reaction or multiple local reactions with different plant foods within the previous year to their recruitment. No oral food challenge (OFC) was performed before starting immunotherapy.

Skin and Serological Tests

The allergy workup included a skin prick test (SPT) for pneumoallergens, plant foods, and panallergens; total IgE (measured with an Immulite 2000 analyzer, Siemens Diagnostics); and serologic sIgE to LTP r*Pru p 3* and other LTP and plant foods (ImmunoCAP, Thermo Fisher, Uppsala, Sweden).

SPT was used to determine sensitization to aeroallergens from grass, *Olea europaea*, *Cupressus arizonica*, and *Platanus acerifolia* pollens, panallergens (e.g., LTP and profilin), and food allergens, including those of peach, other fruits from the *Rosaceae* family (nectarines, apples, and cherries), peanuts, nuts (hazelnuts and walnuts), and other foods involved in the allergic reactions recorded in the patient's medical history. Allergen extracts were provided by ALK-Abelló, S.A. (Madrid, Spain) and Laboratorios Leti S.L.U. (Madrid, Spain). If the extract to a particular plant food was not commercially available, a prick-by-prick test with the offending fresh food was performed. Histamine 10 mg/mL and normal saline solution were used as positive and negative controls, respectively. SPT was performed according to the guidelines of the European Academy of Allergology and Clinical Immunology [13]. The sIgE to LTP peach allergen Pru p 3 was determined by ImmunoCAP® according to the instructions of the manufacturer. The sIgE against Ara h 9 and Cor a 8 were determined in patients allergic to LTPs from peanuts and hazelnuts, respectively. A concentration higher than 0.35 kU/L was considered positive.

Sublingual Immunotherapy

Patients were treated with Pru p 3 SLIT (SLIT *melocotón*, ALK-Abelló S.A., Madrid, Spain) at a concentration of 50 μg/mL. Treatment was initiated at the allergy service on an outpatient basis using a 4-day build-up cluster schedule according to the manufacturer's protocol, shown in Table 1, until reaching a 20-drop dose

Table 1. Build-up schedule of SLIT

Day	Vial	Pru p 3, μg/mL	Drops
1	1	0.05	1
			10
	2	0.5	1
			10
2	3	5	1
			10
3	4	50	1
			2
			5
			10
4			20

Doses were administered at 15-min intervals. Maintenance therapy was performed with a daily dose of 5 drops, corresponding to 12.5 μg of Pru p 3. SLIT, sublingual immunotherapy.

(50 μg). The regimen consisted of several doses per day administered at a 15-min interval. Patients remained under observation for 30 min after the last dose. A maintenance regimen of 5 drops (12.5 μg of Pru p 3) daily was thereafter administered at home for at least 3 years. Adverse reactions were recorded and graded according to the World Allergy Organization classification as reported by Cox et al. [14].

Food Challenge Tests

The effectiveness of SLIT was assessed 1 year after its initiation. The sequence of the assessment was as follows:

1. Open OFC test for unpeeled peach. The challenge was performed following the recommendations of the European Academy of Allergy and Clinical Immunology (EAACI) [15]: Sequential administration of increasing doses at 30-min intervals (5, 20, 40, and 80 g) was performed until a cumulative amount of 145 g (equivalent to a medium-sized peach) has been reached or the patient developed allergic symptoms, the latter indicating a positive OFC. Patients who did not tolerate the total amount of peach were re-tested 6 to 12 months after the first OFC.
2. One month later, patients with a history of peanut and/or nut allergy and negative OFC for unpeeled peach underwent an open OFC test for the responsible food, following the same procedure as for peach, with a starting dose of half a piece (0.5 g), increasing (0.5, 1, 2, 4, and 8) to reach a total amount of peanuts/nuts of 15.5 units (14 g). All challenge tests were performed with peanuts, except for 3 patients, who were challenged with hazelnuts.
3. In the case of a negative OFC, patients were advised to progressively introduce in their diet the fruits and vegetables and peanuts/nuts involved in their allergic reactions. Patients with positive OFC for peanut or nuts were allowed to introduce only fruits and vegetables. Severity of symptoms and food avoidance was recorded after 3 years of SLIT.

Table 2. Baseline characteristics of study patients ($N = 29$)

Demographic characteristics	
Age, mean (IQR), years	24.2 (17–30.4)
Children (<14 yr), *n* (%)	5 (17.2)
Adults, *n* (%)	24 (82.8)
Gender, *n* (%)	
Female	15 (51.7)
Male	14 (48.3)
Clinical characteristics	
SPT results (positive sensitizations), *n* (%)	
Food allergy	
Roseaceae family	29 (100.0)
Other fruits and/or vegetables	8 (27.5)
Peanuts/nuts	21 (72.0)
Pollen allergy	19 (65.5)
Grass	17 (58.6)
Olea europaea	9 (31.0)
Cupressus arizonica	6 (20.7)
None	10 (34.5)
IgE results, KU/L, mean (SD)	622.00 (132.00–718.00)
Specific IgE	
Pru p 3	9.27 (2.92–17.40)
Ara h 9[a]	2.08 (0.87–7.18)
Cor a 8[b]	1.00 (0.40–5.22)
Severity of the allergic reaction[c] to fruits, vegetables, peanuts, and/or nuts, *n* (%)	
Grade 1	3 (10.34)
Grade 2	7 (24.14)
Grade 3	8 (27.59)
Grade 4	10 (34.48)
Grade 5	1 (3.45)

SPT, skin prick test. [a] Calculated over 23 patients. [b] Calculated over 20 patients. [c] According to Sampson grading of food-induced anaphylaxis [16].

Variables and End Points

Demographic and clinical characteristics included age, gender, presence, and type of concomitant pollen allergy, type of foods that triggered the allergic reaction, and the severity of the systemic reaction, classified from grade 1 (the mildest) to grade 5 (most severe) according to Sampson criteria [16] before starting SLIT and as a result of the OFC test 1 year after the treatment start. Number of family plant foods avoided were recorded at the beginning and the end of the study in patients and controls.

Statistics

Quantitative variables were described as the mean, range and standard deviation (SD) or as medians and interquartile range (IQR, defined as percentiles 25 and 75), whereas categorical variables were presented as frequencies and percentages. Bivariate analyses were performed using non-parametric Mann-Whitney U test for assessing differences between groups with and without SLIT. p values <0.05 were considered significant. All analyses were performed using the SPSS package (IBM SPSS Statistics for Windows, Version 20.0., IBM Corp, Armonk, NY, USA).

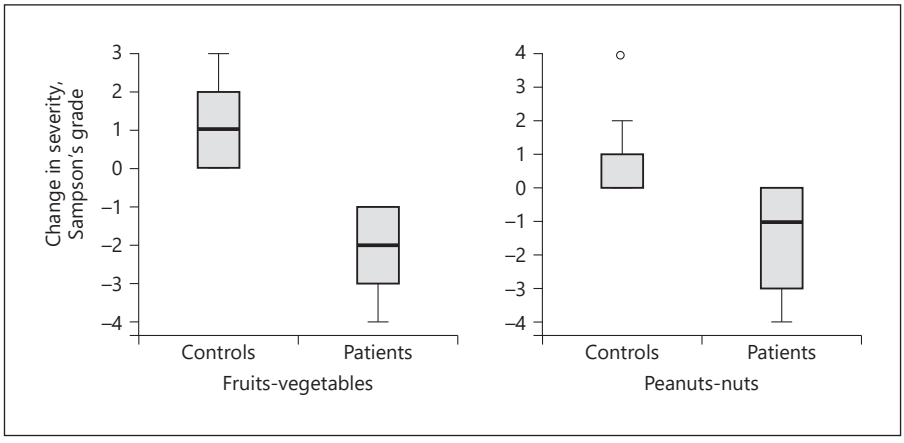

Fig. 1. Changes in severity of symptoms with LTP foods. LTP, lipid transfer protein.

Results

Characteristics of Study Patients

A total of 29 patients started LTP SLIT within the investigated period: 14 men and 15 women. Five (17.2%) of them were children and 24 (82.8%) adults, with a mean age of 24.7 years (range 5.5–43.1). Table 2 summarizes the demographic and clinical characteristics of study patients. All patients were allergic to fruits from the *Rosaceae* family, and most of them had also experienced symptoms with peanut and/or nut intake; allergic reactions to other families of fruits and vegetables were present in nearly 30% of patients. Regarding the severity of food-allergic systemic reactions, two thirds (65.6%) corresponded to the severe grades (3–5) according to Sampson's criteria, irrespective of whether the allergen was a fruit, a vegetable, peanut, or a nut. Up to 65.5% of the patients presented pollen allergy, mostly grass pollen. None of them had previously received pollen immunotherapy.

Control group comprised 9 women and 4 men, with a median age of 13.73 years (IQR 7.64–27.81 years). Thirty-eight percent were children. Eight patients (61%) presented severe reactions (grades 3–4) with *LTP* foods.

Safety of SLIT

Of all patients starting LTP SLIT, 7 (24%) discontinued immunotherapy within the first year due to either poor compliance ($n = 4$, 13.8%) or adverse reactions ($n = 3$, 10.3%), which consisted in dysphagia and facial angioedema after administering the first maintenance dose, intense physical discomfort along with oral pruritus and digestive discomfort during the first month of treatment, and increase in blood pressure and menstrual disorders after 6 months of SLIT, both of which were resolved after treatment interruption. Twenty-one patients (72.4%) reported mild oral pruritus with drops administration during the first weeks, which spontaneously resolved within the few minutes following administration. No other adverse events were reported during SLIT.

Follow-Up in Patients with LTP Immunotherapy and Controls

Of the 22 patients who completed the 3 years of SLIT, 16 (72.7%) had negative results for peach OFC after the first year. Of the 6 patients with a positive challenge, 5 showed no reaction in a second OFC test: 3, after 6 months; 1, after 1 year; and 1, after 16 months from the first OFC due to pregnancy. One patient experienced a positive reaction again. Thus, the global SLIT desensitization rate in 2 years increased to 95%. Furthermore, of the 16 patients who were allergic to peanuts and/or nuts, 11 (68.7%) had negative OFC results (10 to peanuts and 1 to hazelnuts), whereas 5 presented allergic reactions when tested: 2 with hazelnuts and 3 with peanuts.

The 13 patients from the control group were followed up during a period of 3.75 years (range 2.8–6.9 years). During this time the severity of the reactions presented with accidental food ingestion, using Sampson's grading system, increased with fruits and vegetables (from 1.42 to 2.17) and with peanuts/nuts (from 1.81 to 2.32). We found a significative difference ($p < 0.001$) when we compare the decrease in the grade of symptoms in patients (−2.04 for fruits/vegetables and −1.59 for peanuts/nuts) and the increase in controls (1.07 and 0.84 respectively) from the beginning to the end of the study with all kind of plant foods as it is shown in Figure 1.

All patients went on receiving SLIT to complete 3 years. Regarding the progression of their food allergy af-

Table 3. Clinical and demographic data for the total of patients who received LTP SLIT

ID No.	Gender	Age	Pollen allergy	Fruit/vegetable allergy	Peanut/ nut allergy	Sampson's grade†	Total IgE	sIgE			Peach OFC	Peanut/ nut OFC
								rPru p 3	rAra h 9	rCor a 8		
1#	M	19.1	+	*Rosaceae* and kiwi	Almond	4	626	69.8	nd	nd	nd	nd
2	M	36.5	–	*Rosaceae*	Peanut, sunflowert seeds	3	132	30.82	28.79	0	–	–
3	F	33.6	+	*Rosaceae*	No	1	50	0.92	nd	nd	–	na
4	F	17.0	–	*Rosaceae* and green beans	Peanut, walnut	3	210	4.32	1.85	0.44	–	+
5#	F	26.7	–	*Rosaceae*	No	2	438	90.3	6.95	nd	nd	nd
6	F	25.9	–	*Rosaceae*, tomato, lettuce, and pepper	No	1	308	1.56	0.83	nd	–	na
7#	M	19.9	–	*Rosaceae*, tangerine, cherry, and tomato	Almond	1	88	3.47	nd	nd	nd	nd
8#	F	17.5	+	*Rosaceae*	Peanut	3	766	16.3	nd	nd	nd	nd
9	M	20.4	+	*Rosaceae*	Peanut, hazelnut	4	1,000	17.4	2.54	8.27	–	–
10#	M	26.5	+	*Rosaceae* and eggplant	Peanut	3	nd	11.8	10.6	8.5	nd	nd
11	M	30.4	+	*Rosaceae*	Peanut, walnut	4	507	6.72	2.08	0.78	–*	–
12	F	25.2	+	*Rosaceae*, tomato, lettuce, carrot, corn, and beet	Peanut, hazelnut	1	104	19.20	12.9	18.10	–	–
13#	F	38.6	–	*Rosaceae*	Walnuts	4	78	1.82	0.86	0.23	nd	nd
14	M	30.9	+	*Rosaceae*, kiwi, lentil, and chicken peas	Peanut, hazelnut	4	2,473	13.00	8.17	3.70	–	–
15	M	11.6	+	*Rosaceae*	Hazelnut	4	718	15.10	nd	4.29	–	+‡
16	F	17.1	+	*Rosaceae*, lettuce, and asparragus	Peanut, hazelnut	3	25.5	3.72	0.65	0.85	–	–
17	F	33.3	+	Rosaceae, kiwi, mango, green beans, and lentil	Peanut	2	226	9.27	2.77	0.19	–*	–
18	M	5.6	+	*Rosaceae*	Peanut	2	157	9.30	2.54	1.32	–	–
19	M	26.8	–	*Rosaceae*	Peanut	3	73	0.55	0.53	0.16	–	+
20	F	35.0	–	*Rosaceae* and kiwi	Peanut, hazelnut, almond	3	845	5.75	3.99	1.05	–*	+
21	F	25.6	+	*Rosaceae*	Hazelnut, almond	5	485	1.13	0.63	nd	–	+‡
22#	F	22.2	+	*Rosaceae*, grapes, and avocado	Almomd, walnuts, hazelnuts	1	nd	32.4	1.63	1.44	nd	nd
23	F	43.2	+	*Rosaceae*	No	2	114	4.51	nd	nd	–	na
24	M	6.8	–	Rosaceae, banana, tangerine, pear, lombarda, and cabbage	Hazelnut, walnut, cashew	4	1,156	>100	62.4	22.8	–*	–
25	F	13.3	+	*Rosaceae*	Peanut	1	55	2.32	2.00	0.94	–	–
26	M	24.1	+	*Rosaceae*, lentil, and chicken peas	Hazelnut	3	675	2.35	0.95	0.16	–	–‡

LTP, lipid transfer protein; SLIT, sublingual immunotherapy; sIgE, specific IgE; OFC, oral food challenge; nd, not done; na, not apply; +,: positive; –, negative. † Patients' symptoms according to the Sampson's classification for food allergy reactions. # Patients discontinued immunotherapy before one year so OFC was not performed. All the rest completed 3 years of SLIT. * The patient had a positive result to OFC after a year of immunotherapy but a negative one after 18-24 months of immunotherapy. ‡ The patient was challenged with hazelnut.

Int Arch Allergy Immunol 2021;182:447–454
DOI: 10.1159/000512613

ter receiving SLIT, by the time of submitting the manuscript, of the 21 patients with negative OFC tests, 20 were having a normal diet with all types of fruits and vegetables, including those plant foods they did not tolerate previously. No allergic symptoms were recorded. The remaining patient does not eat *Rosaceae* fruits for fear of allergic reactions. Correspondingly, the 11 patients with negative OFC to peanut and/or nuts can eat them without showing any allergic reaction. The 5 patients with positive challenge tests still cannot eat peanuts or nuts although they tolerate traces (<2% of the total food) that they did not tolerate before SLIT. None of the patients had developed symptoms with new foods. The details regarding clinical data and OFC results are shown in Table 3. No changes in pollen symptoms were observed in patients receiving *Pru p* 3 SLIT.

All the patients but one included in the control group developed allergic reactions after accidental plant foods containing LTP (*Rosaceae* fruits, peanuts, nuts, lettuce…) intake during the period of study. For this reason, we considered it was not necessary to perform the challenge test except for this one; an OFC with unpeeled peaches was performed with a positive result (generalized urticaria) in this case.

At the end of the follow-up period, the patients from the control group had a restricted diet, avoiding fruits from *Rosaceae* family in all cases, peanuts in 8, nuts in 7, other legumes in 2, and other vegetables in 2 cases. Seven out of 13 controls had experienced allergic reactions with new foods. So, the number of families of plant food involved in the allergic symptoms (Rosaceae fruits, other fruits, vegetables, peanuts and legumes, nuts…) raised the median from 1.37 to 2.08.

Discussion

In this study, we found that, after 1 year of Pru p 3 SLIT administered under routine practice conditions, 95% of the patients who had experienced previous systemic allergic reactions in response to the intake of plant foods containing LTPs developed good tolerance to peach; 69% of the patients also tolerated peanuts and/or nuts. Moreover, none of the patients who subsequently presented negative OFC results have experienced allergic reactions after including the fruits, vegetables, peanuts, or nuts (previously not tolerated) in their routine diet. These data are relevant when comparing with the control group as far as the patients who did not start SLIT developed several allergic reactions with the accidental intake of plant food containing LTP and at the end of the study all of them still had a restricted diet avoiding several families of plant foods containing LTP in most cases.

The increased tolerance to peach observed in most patients after 1-year treatment with Pru p 3 SLIT was consistent with previous studies – including randomized clinical trials – that assessed the efficacy of a Pru p 3 SLIT during 6 or 12 months [10–12, 17], most of which also reported a reduction of the wheal diameter in SPT [10, 12, 17]. In addition, open OFCs showed that 1 year of Pru p 3 SLIT not only improved tolerance to *Rosaceae* fruits but also to peanuts. This effect is consistent with the findings of Gómez et al. [12], who observed an improvement in peanut tolerances after 1 year of treatment with Pru p 3 SLIT, presumably due to cross-reactivity between LTPs Pru p 3 and Ara h 9 [18, 19]. Our analysis showed high effectiveness of Pru p 3 SLIT in peanut sensitization; however, as reported by Gómez et al. [12], the peanut desensitization rate did not reach that achieved with *Rosaceae* allergies. This partial effectiveness in peanut or nut allergy could be attributed to other allergens involved in these allergies besides LTPs, such as globulins or 2S albumins [20–22]. In this regard, our working protocol has been modified over time in order to assess other allergens responsible for peanut and/or nut sensitization prior to the administration of the immunotherapy (data not shown). On the other hand, we found a high peanut tolerance (i.e., 76%), even higher than that reported in a previous study after a 44-week peanut SLIT [23]. This finding suggests that a Pru p 3 SLIT could reach the same efficacy as a peanut SLIT to desensitize against peanuts when the LTP Ara h 9 is the sensitizing peanut allergen.

In our analysis, Pru p 3 SLIT showed a good tolerability and safety profile in most patients, with no adverse events reported in those who completed the immunotherapy. Previous studies investigating Pru p 3 SLITs also presented a good safety profile although more than half of patients showed some adverse reactions to treatment during the build-up phase, mainly oral allergy symptoms that disappeared during the maintenance phase of the therapy [10, 12].

One study's limitation was the lack of OFC assessments before SLIT; however, considering that all patients in our analysis had experienced either an anaphylactic reaction or confirmed allergic reactions to multiple foods 1 year before the study start, this approach was considered potentially harmful. On the other hand, our work was based on a prospective study with a similar sample size than other studies with Pru p 3 SLIT. Of note, whereas most of the studies included patients over 18 years of age,

our analysis also included minors; therefore, the results of our study may apply to children and adolescent allergic patients – though we must admit that the small sample may limit the statistical power of the analysis. It is also worth mentioning that, unlike most of the studies investigating the efficacy of Pru p 3 SLIT, which excluded patients with previous anaphylactic reactions, our analysis was focused on these patients, thus deepening into the effectiveness of the therapy in various patient profiles. In this regard, the results of our study are relevant to treat those patients who might benefit from this treatment but also those that are often excluded from receiving immunotherapy because they are considered patients at high risk of severe adverse events.

Conclusions

Our results support the administration of a Pru p 3 SLIT in patients who are allergic to LTPs from plant foods and experienced reactions in response to the intake of fruits, vegetables, and even peanuts or nuts. The time framework of our study prevents drawing conclusions regarding the transient or permanent nature of the tolerance observed (to this end, an observation period without purposeful exposure and subsequent OFC shall be included). It has been documented that 27% of the patients with LTP syndrome eventually experience new food allergies, thus presenting local or systemic symptoms following the ingestion of previously tolerated foods [24]. This happened in 7 out of 13 patients (53.8%) of our control group. However, our work aimed to avoid a restrictive diet while preventing the risk of allergic reactions in our patients, and this objective has been mostly achieved, compared to the control group. We have encouraged our patients to keep on the daily plant food intake to ensure LTP administration. Further research is needed to determine the results in terms of long-term tolerance after Pru p 3 SLIT and to know which is the best immunotherapy for patients who have a peanut or nut allergy, as other allergens apart from LTPs are likely to be involved, and Pru p 3 SLIT may fail to completely desensitize against peanut or nut ingestion.

Acknowledgements

The authors would like to thank Dr. Belen Mateo, Ana M.ª Sanz, and Isabel de Mingo for their help during the study conduction and Miguel Torralba for his statistical assistance. Gerard Carot-Sans, PhD, provided editorial support on behalf of BioClever 2005 during the preparation of the manuscript.

Statement of Ethics

The study protocol was approved by the Independent Ethics Committee of Guadalajara (Spain), and all patients signed the corresponding informed consent to participate.

Conflict of Interest Statement

J.M.B. reports personal fees for lectures from ALK, Diater, Leti, and Chiesi and fees for investigation from Diater outside the submitted work. A.V.C. reports personal fees for lectures from ALK, Diater, Novartis, Allergy Therapeutics, and Leti and fees for investigation from Diater and Novartis outside the submitted work. R.C. reports personal fees for lectures from Novartis and Chiesi and fees for investigation from Diater and Novartis outside the submitted work. M.I.P. reports personal fees from ALK, Leti, Diater, and Roxal outside the submitted work.

Funding Sources

The authors did not receive any funding.

Author Contributions

J.M.B. and A.V.C. made substantial contributions in the study design, data analysis, and data interpretation. J.M.B., A.V.C., R.C., and M.I.P. substantially contributed to data acquisition. The manuscript was drafted by J.B.M., A.V.C., R.C., and M.I.P. and further revised by J.M.B. and A.V.C. All co-authors approved the final version of the manuscript before submitting it.

Availability of Data and Material

The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

References

1 Cuesta-Herranz J, Lázaro M, Figueredo E, Igea JM, Umpiérrez A, De-Las-Heras M. Allergy to plant-derived fresh foods in a birch- and ragweed-free area. Clin Exp Allergy. 2000;30(10):1411–6.
2 Fernández-Rivas M, Bolhaar S, González-Mancebo E, Asero R, van Leeuwen A, Bohle B, et al. Apple allergy across Europe: how allergen sensitization profiles determine the clinical expression of allergies to plant foods. J Allergy Clin Immunol. 2006;118(2):481–8.
3 Asero R, Antonicelli L, Arena A, Bommarito L, Caruso B, Colombo G, et al. Causes of food-induced anaphylaxis in italian adults: a Multi-Centre Study. Int Arch Allergy Immunol. 2009;150(3):271–7.

4 Asero R, Antonicelli L, Arena A, Bommarito L, Caruso B, Crivellaro M, et al. EpidemAAI-TO: features of food allergy in Italian adults attending allergy clinics: a multi-centre study. Clin Exp Allergy. 2009;39(4):547–55.
5 Asero R, Piantanida M, Pinter E, Pravettoni V. The clinical relevance of lipid transfer protein. Clin Exp Allergy. 2018;48(1):6–12.
6 Rial MJ, Sastre J. Food allergies caused by allergenic lipid transfer proteins: what is behind the geographic restriction? Curr Allergy Asthma Rep. 2018;18(11):56.
7 Rodrigues-Alves R, Lopez A, Pereira-Santos MC, Lopes-Silva S, Spínola-Santos A, Costa C, et al. Clinical, anamnestic and serological features of peach allergy in Portugal. Int Arch Allergy Immunol. 2009;149(1):65–73.
8 Salcedo G, Sanchez-Monge R, Diaz-Perales A, Garcia-Casado G, Barber D. Plant non-specific lipid transfer proteins as food and pollen allergens. Clin Exp Allergy. 2004;34(9):1336–41.
9 Pascal M, Muñoz-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;42(10):1529–39.
10 Fernández-Rivas M, Garrido Fernández S, Nadal JA, Díaz de Durana MD, García BE, González-Mancebo E, et al. Randomized double-blind, placebo-controlled trial of sublingual immunotherapy with a Pru p 3 quantified peach extract. Allergy. 2009;64(6):876–83.
11 Garrido-Fernández S, García BE, Sanz ML, Echechipía S, Lizaso MT, Tabar AI. Are basophil activation and sulphidoleukotriene determination useful tests for monitoring patients with peach allergy receiving sublingual immunotherapy with a Pru p 3-enriched peach extract? J Investig Allergol Clin Immunol. 2014;24(2):106–13.
12 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;47(3):339–50.
13 Skin tests used in type I allergy testing position paper. Sub-committee on skin tests of the European Academy of Allergology and clinical immunology. Allergy. 1989;44(s10):11–59.
14 Cox L, Larenas-Linnemann D, Lockey RF, Passalacqua G, Sanchez-Borges M, Lockey RF. Speaking the same language: the world allergy organization subcutaneous immunotherapy systemic reaction grading system. J Allergy Clin Immunol. 2010;125(3):569–e7.
15 Bindslev-Jensen C, Ballmer-Weber BK, Bengtsson U, Blanco C, Ebner C, Hourihane J, et al. Standardization of food challenges in patients with immediate reactions to foods: position paper from the European Academy of Allergology and clinical immunology. Allergy. 2004 Jul;59(7):690–7.
16 Sampson HA. Anaphylaxis and emergency treatment. Pediatrics. 2003;111(6 Pt 3):1601–8.
17 García BE, González-Mancebo E, Barber D, Martín S, Tabar AI, Díaz de Durana AM, et al. Sublingual immunotherapy in peach allergy: monitoring molecular sensitizations and reactivity to apple fruit and Platanus pollen. J Investig Allergol Clin Immunol. 2010;20(6):514–20.
18 Lauer I, Dueringer N, Pokoj S, Rehm S, Zoccatelli G, Reese G, et al. The non-specific lipid transfer protein, Ara h 9, is an important allergen in peanut. Clin Exp Allergy. 2009;39(9):1427–37.
19 Javaloyes G, Goikoetxea MJ, García Nuñez I, Aranda A, Sanz ML, Blanca M, et al. Pru p 3 acts as a strong sensitizer for peanut allergy in Spain. J Allergy Clin Immunol. 2012;130(6):1432–e3.
20 Bublin M, Breiteneder H. Cross-reactivity of peanut allergens. Curr Allergy Asthma Rep. 2014;14(4):426.
21 Costa J, Mafra I, Carrapatoso I, Oliveira MB. Hazelnut allergens: molecular characterization, detection, and clinical relevance. Crit Rev Food Sci Nutr. 2016;56(15):2579–605.
22 Costa J, Carrapatoso I, Oliveira MB, Mafra I. Walnut allergens: molecular characterization, detection and clinical relevance. Clin Exp Allergy. 2014;44(3):319–41.
23 Fleischer DM, Burks AW, Vickery BP, Scurlock AM, Wood RA, Jones SM, et al. Sublingual immunotherapy for peanut allergy: a randomized, double-blind, placebo-controlled multicenter trial. J Allergy Clin Immunol. 2013;131(1):119–7.
24 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;50(4):156–62.