ABSTRACT:

Sublingual immunotherapy with Pru p3 extract (SLIT-peach®) is used in allergy patients to multiple plant foods to induce tolerance to nonspecific lipid transfer proteins (nsLTP). The aim of this paper is to communicate the efficacy of a new ultrafast regimen. Until now on the initiation regimen lasts four days. We present a number of 22 patients with LTP-syndrome due to ingestion of different vegetable foods sensitized to Pru p3. According to European Academy of Allergy position paper (1) food immunotherapy is indicated when avoidance measures are ineffective, undesirable, or cause serious limitations on patients quality of life. Our patients had an impact on their quality of life (score >130) before SLIT measured with (2) EuroPrevall Food Allergy Quality of Life Questionnaire (FAQLQ). The ultrafast regimen in one day is achieved in the 95% of our patients. Mild adverse reactions where observed, such as oral pruritus presence in almost all patients. Only one patient (5%) achieved the maintenance dose in two days due to intense oral pruritus. None patients presented systemic reactions. The maintenance dose achieved consists of 4 drops (0,16 ml) from vial number 4 daily. The concentration of Pru p3 in vial nº4 is 50 μcg/ml. Four drops a day equals 8 micrograms of Pru p3. This new ultrafast regimen in one day is secure in patients with LTP-Syndrome to induce tolerance to SLIT-peach ® (Pru p3 extract).

Keywords: food allergy, anaphylactic LTP-Syndrome, Pru p3, SLIT, tolerance, panallergen, sublingual immunotherapy, induction, Ultrafast regimen.

Impact statement: Cluster therapies in sublingual immunotherapy are nowadays our aim to achieve in a short period time the maintenance dose. Mild adverse reactions are observed as oral pruritus. We present this efficient new regimen to induce tolerance to SLIT-peach in one day.

INTRODUCTION:

Allergy immunotherapy (AIT) has been practiced for more than a hundred years. Repeated low doses of allergen induce clinical tolerance and improve quality of life in patients with respiratory allergy (3). AIT may increase the remission rate of asthma and sensitization to new allergens (4). The route chosen for immunotherapy with aeroallergens can be oral, subcutaneous or sublingual. Subcutaneous immunotherapy is worldwide extended with respiratory patients in the allergy office. Oral tablets are used in patients with house dust-mite allergy with good results (5). Food allergy immunotherapy has been practiced in the latest 10 to 15 years using oral and sublingual route. The prevalence and incidence of food allergy is significantly increasing in recent years. Patients are allergic to different food depending on the area where they live (6). Lipid transfer proteins (LTPs) are a very common panallergen in the Mediterranean area. LTPs are very ubiquitous in the plant kingdom. The resistance to pepsin and to chemical digestion is a quality to produce anaphylactic reactions. Patients with LTP-syndrome are often seen in our office (7). Allergens presented in peach, *Prunus persica*, are well known. Pru p3 is a nonspecific lipid transfer protein (nsLTP) present in peach and associated to severe systemic symptoms. Patients with LTP-syndrome have IgE against Pru p3 and often experience crossed reactivity to other nsLTP present in other fruits, or nuts, cereals, veggies and legumes. Our patients presented crossed reactivity to walnuts, peanuts, hazelnuts, *rosaceae* fruits, lettuce and tomato. Sublingual immunotherapy with SLIT-peach® is a commercial extract of concentred Pru p3. Patients with LTP-syndrome have often anaphylactic reactions to hidden food allergens (8). Wide dietary restrictions in these patients reduce their quality of life. In this context it is necessary to use an etiological treatment (immunotherapy) to increase tolerance to ingesting foods involved. Immunotherapy in food allergy is recently approved for peanut in the U.S (9). Several clinical *thesis* have published the improvement of quality of life after sublingual immunotherapy with SLIT-peach ® Pru p3.

The manufacture´s standard initiation protocol for SLIT-peach ® has duration of 4 days (Table I). A fast regimen is been published with a duration of two days (Table II) by the group of Pereira in 2019. We proposed an ultra-fast regimen in one day (Table III).

MATERIAL AND METHODS:

We selected 22 patients with LTP-Syndrome, 15 women and 7 men. Ages are between 19 and 43 years old. All our patients had severe anaphylactic reactions to different plant-foods. Inclusion criteria were: unequivocal clinical history of allergy to peach and/or other fruits containing LTP, one or more episodes of anaphylaxis following the ingestion of fruits, nuts or vegetables containing LTP. Oral provocation tests were not performed since all patients had anaphylactic episodes after the ingestion of food containing LTP in the previous year and also declined a challenge that could induce a new anaphylaxis. We measured the severity reactions with the ordinal food allergy severity score (oFASS-5). Five of them presented reactions oFASS grade 5 (22%). Fourteen of them presented oFASS grade 4 (63%). The severity score oFASS grade 3 was for 3 patients (13%). Quality of life was measured with the EuroPrevall Food Allergy-Quality of Life Questionnaire (FAQLQ). This consists in a 29 items questionnaire with a maximum of 174 score. The score for quality of life in our patients was between 170 and 131 with a media of 150,5 score. All of our patients had a restricted diet due to crossed reactivity. Skin pricks tests and IgE against Pru p3 where performed according to the standardized European protocols (10) and results where positive in all patients (diameter papule > 3 mm compared to the negative control). Serum specific IgE to Pru p3 was higher than 3.47 KU/L in all of our patients. IgG4 against *Pru p3* was measured before inducing tolerance. Monitoring IgG4 is relevant in these patients, especially as it is a biomarker of compliance to treatment in SLIT. Molecular diagnose under Microarray with Immuno Solid-Phase Allergen Chip (ISAC ®) and total IgE, where performed in blood tests in all patients. The results are showed in figure 1. Specific serum IgE where positive to seven nsLTPs in 40% of our patients (9 out of 22): Ara h9, Cor a8, Jur r3, Pru p3, Art v3, Ole e7, Pla a3. Seven from 22 patients, 31.8%, where positive to six nsLTP: Ara h9, Cor a8, Jur r3, Pru p3, Art v3, Ole e7. Five of 22 patients, 22.7%, where positive to five ns LTP: Ara h9, Cor a8, Jur r3, Pru p3, Art v3. And only one patient out of 22, 4.5%, was positive to 4 nsLTP: Ara h9, Cor a8, Jur r3, Pru p3. Results are showed in table 4. Blood tests were performed before SLIT, with a total IgE between 375 KU/L and 123 KU/L with an average of 249 KU/L and serum IgE against Pru p3 was between 53.9 KU/L and 3.47 KU/L with an average of 28.6 KU/L (Figure 1). All patients underwent the administration in clinical office of the ultrafast regimen designed in our service according to Table III.

Results: 21 patients achieved tolerance in one day with our proposed regimen (95.45 %) and only 1 patient needed the rapid regimen of 2 days, for presenting intense oral syndrome, not presenting systemic reactions. None of our patients presented systemic reactions. The total dose of Pru p3 received in one day with the ultrafast regimen is 16.442 mcg. The maintenance dose is 8 mcg of Pru p3 daily (4 drops).

Discussion: Cluster doses in one day are safe and fast to induce tolerance to SLIT-peach ® in patients with history of anaphylaxis to Pru p3. The ultra-fast regimen in one day has already been published (11) as a case report. Our series is a prospective study about 22 patients, with a cumulative dose of 16,442 μcg (2 hours and 15 minutes duration) and a daily maintenance dose of 8 μg of Pru p3. The daily application at home proposed makes a cumulate dose of 1440 μcg of Pru p3 in six months. There is another paper with this ultra-fast regimen of administration for peach-ALK slit vaccine that achieves the maintenance dose in one day, but also repeats this dose in a second visit. It has also been published by Pereira and cols (12) in 2019. The number of patients in the active group in this case is n=10. The cumulative dose achieved in one day in this series was 47 μcg of Pru p3, this is superior compare to our group. We proposed a modified regimen only in one day and a daily maintenance dose. The aim of this regimen is to reduce the time of hospital administration to 1 day. Monitoring IgG4 is relevant in these patients, especially as it is a biomarker of compliance to treatment in SLIT.

CONCLUSIONS: SLIT with Pru p3 extract is secure in patients with LTP-syndrome even for patients with severe symptoms, such as anaphylaxis. Cluster administration in one day is well tolerated. Severity score oFASS does not predict tolerance to SLIT-peach in patients with LTP-syndrome.

CONFLICT OF INTERESTS: All authors declare that they don´t have any conflict of interests.

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Table I. SLIT in 4-days (Conventional regime). Fernandez Rivas 2009. *Once the dose is achieved, maintenance dose will be administered at home: 5 drops from bottle 4, daily. Cumulative dose in the initial phase is: 78,442 mcg. The cumulative dose in six months is 1800 mcg of Pru p3.

DAY	VIAL	Concentration mcg/ml of Pru p3	DROPS	Dosage of Pru p3 (mcg)	TIME between administration (min)
Day 1	Vial 1	0.05	1	0.002	15
			10	0.02	
	Vial 2	0.5	1	0.02	15
			10	0.2	
Day 2	Vial 3	5	1	0.2	15
			10	2	
Day 3	Vial 4	50	1	2	15
			2	4	
			5	10	
			10	20	
Day 4	Vial 4	50	20	40	Unique adminitration

***Daily at home, maintenance dose: 5 drops from bottle 4 (10 mcg of Pru p3).**

Table II. SLIT in 2 days (Fast regime Pereira 2019) *Once the dose is achieved maintenance dose will be administered at home: 5 drops from bottle 4, daily. Cumulative dose in one day 31,92 mcg of Pru p3. The cumulative dose in six months is 1800 mcg of Pru p3.

DAYS	VIAL Mcg/ml	DROPS	Mcg of Pru p3	Time between administrations (min)
Day 1	Vial 2 0.5	1	0.02	30
		5	0.1	
	Vial 3 5	1	0.2	30
		3	0.6	
		5	1	
	Vial 4 50	1	2	30
		2	4	
		3	6	
		4	8	
		5	10	
Day 2	Vial 4 50	3	6	60
		5	10	

***Daily at home, maintenance dose: 5 drops from bottle 4 (10 mcg of Pru p3).**

Table III. SLIT in one day (ultrafast regimen). *Once the dose is achieved, maintenance dose will be administered at home 4 drops from bottle 4, daily. This dose equals 8 mcg per day of pru p3. Cumulative dose in one day: 16,46 mcg or Pru p3. The cumulative dose in six months is 1440 mcg of Pru p3.

VIAL	Concentration of Pru p3 (mcg/ml)	DROPS	Total Pru p3 mcg	TIME between administration (min)
Vial 1	0.05	1	0.002	15 min
		10	0.02	
Vial 2	0.5	1	0.02	15 min
		10	0.2	
Vial 3	5	1	0.2	15 min
		10	2	
Vial 4	50	1	2	15 min
		2	4	
		4	8	

* **Daily at home, maintenance dose** 4 drops from bottle 4.