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# Ultrafast regimen for Pru p3 sublingual immunotherapy (SLIT-Peach®) in patients with anaphylactic LTP-Syndrome

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**Key words**

*Ultrafast regimen; lipid transfer proteins; food allergy; rPru p3; sublingual immunotherapy.*

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**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.*

***Summary***

*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 were 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. No 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 number 4 is 50 µg/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).*

## 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 last 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 of-

***Table I*** *- SLIT in 4-days (conventional regime) (13).*

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

Once the dose is achieved, maintenance dose will be administered at home: 5 drops from bottle 4, daily (10 µg of Pru p3). Cumulative dose in the initial phase is: 78,442 µg. The cumulative dose in six months is 1,800 µg of Pru p3.

fice (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 cross-reactivity to other nsLTP present in other fruits, or nuts, cereals, veggies and legumes. Our patients presented cross-reactivity to walnuts, peanuts, hazelnuts, Rosaceae fruits, lettuce and tomato. Sublingual immunotherapy with SLIT-peach® is a commercial extract of concentrated 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

***Table II*** *- SLIT in 2 days (fast regimen, ref. 12).*

| Days | Vial µg/ml | Drops | µg of Pru p3 | Time between administrations (min) |
|---|---|---|---|---|
| 1 | 2 | 1 | 0.02 | 30 |
| | 0.5 | 5 | 0.1 | - |
| | 3 | 1 | 0.2 | 30 |
| | 5 | 3 | 0.6 | - |
| | | 5 | 1 | - |
| | 4 | 1 | 2 | 30 |
| | | - | - | - |
| | | 2 | 4 | - |
| | | 3 | 6 | - |
| | | 4 | 8 | - |
| | 50 | 5 | 10 | - |
| 2 | 4 | 3 | 6 | 60 |
| | 50 | - | - | - |
| | | 5 | 10 | - |

Once the dose is achieved maintenance dose will be administered at home: 5 drops from bottle 4, daily (10 µg of Pru p3). Cumulative dose in one day 31.92 µg of Pru p3. The cumulative dose in six months is 1,800 µg of Pru p3.

***Table III*** *- SLIT in one day (ultrafast regimen).*

| Vial | Concentration of Pru p3 (µg/ml) | Drops | Total Pru p3 µg | Time between administration (min) |
|---|---|---|---|---|
| 1 | 0.05 | 1 | 0.002 | 15 min |
| | | 10 | 0.02 | |
| 2 | 0.5 | 1 | 0.02 | 15 min |
| | | 10 | 0.2 | |
| 3 | 5 | 1 | 0.2 | 15 min |
| | | 10 | 2 | |
| 4 | 50 | 1 | 2 | 15 min |
| | | 2 | 4 | |
| | | 4 | 8 | |

Once the dose is achieved, maintenance dose will be administered at home 4 drops from bottle 4, daily. This dose equals 8 µg per day of Pru p3. Cumulative dose in one day: 16.46 µg of Pru p3. The cumulative dose in six months is 1,440 µg of Pru p3.

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 doctoral dissertations 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 a duration of 4 days (**table I**). A fast regimen has been published with a duration of two days (**table II**) by the group of Pereira in 2019. We propose an ultra-fast regimen in one day (**table III**).

**Case presentation**

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 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 of 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 our patients had a restricted diet due to cross-reactivity. Skin pricks tests and specific IgE against Pru p3 were performed according to the standardized European protocols (10) and results were 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 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 diagnosis under Microarray with Immuno Solid-Phase Allergen Chip (ISAC®) and total IgE, were performed in blood tests in all patients. The results are showed in **table IV**.

Specific serum IgE was 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%, were positive to six nsLTP: Ara h9, Cor a8, Jur r3, Pru p3, Art v3, Ole e7. Five of 22 patients, 22.7%, were 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 IV**. 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 (**table IV**). All patients underwent the administration in the clinical office of the ultrafast regimen designed in our service according to **table III**.

**Results**

Twenty-one 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 µg. The maintenance dose is 8 µg of Pru p3 daily (4 drops).

***Table IV*** *- Clinical data.*

| Age | Gender | FASS5 | FAQLQ | IgE total | IgE to Pru P3 | IgG4 to Pru P3 | ISAC (Nº LTP) | Ultrafast | Swallowed |
|---|---|---|---|---|---|---|---|---|---|
| 19 | Male | Grade 4 | 137 | 234 | 7.23 | 0.1 | 7 | Yes | Yes |
| 24 | Male | Grade 4 | 131 | 257 | 5.65 | 0.02 | 6 | Yes | Yes |
| 27 | Female | Grade 3 | 146 | 123 | 11.34 | 0.7 | 6 | Yes | Yes |
| 33 | Female | Grade 4 | 165 | 254 | 13.4 | 1.01 | 7 | Yes | Yes |
| 41 | Female | Grade 5 | 170 | 176 | 52.08 | 1.2 | 7 | Yes | Yes |
| 19 | Female | Grade 4 | 166 | 201 | 21.5 | 0.23 | 7 | Yes | Yes |
| 32 | Female | Grade 3 | 142 | 126 | 3.47 | 0.01 | 6 | Yes | Yes |
| 35 | Male | Grade 4 | 153 | 327 | 17.23 | 0.8 | 7 | Yes | Yes |
| 23 | Female | Grade 4 | 146 | 251 | 7.34 | 0.1 | 7 | Yes | Yes |
| 26 | Female | Grade 3 | 161 | 168 | 6.74 | 0.2 | 7 | Yes | Yes |
| 33 | Male | Grade 4 | 142 | 248 | 32.7 | 0.6 | 6 | Yes | Yes |
| 41 | Male | Grade 4 | 139 | 351 | 18.7 | 1.08 | 7 | Yes | Yes |
| 18 | Female | Grade 5 | 146 | 198 | 45.8 | 0.23 | 5 | Yes | Yes |
| 23 | Female | Grade 4 | 153 | 289 | 35.8 | 0.1 | 5 | Yes | Yes |
| 43 | Female | Grade 4 | 153 | 341 | 23.9 | 0.2 | 5 | Yes | Yes |
| 42 | Male | Grade 4 | 162 | 246 | 53.9 | 0.7 | 6 | Yes | Yes |
| 32 | Female | Grade 4 | 137 | 256 | 24.1 | 1.01 | 4 | Yes | Yes |
| 41 | Female | Grade 4 | 131 | 234 | 12.8 | 0.3 | 5 | Yes | Yes |
| 37 | Male | Grade 5 | 166 | 197 | 58.9 | 0.1 | 6 | Yes | Yes |
| 28 | Female | Grade 5 | 170 | 329 | 28.91 | 0.7 | 7 | No/two days | Yes |
| 39 | Female | Grade 4 | 140 | 247 | 8.91 | 0.6 | 6 | Yes | Yes |
| 19 | Female | Grade 3 | 132 | 375.6 | 13.4 | 0.28 | 5 | Yes | Yes |

Ordinal food allergy severty score: oFASS-5, grade 1 includes reactions restricted to the oral cavity; grades 2 to 5 may include oral symptoms, but other target organs are affected. Grading is based on the organ/system involved regardless of the type or number of specific symptoms present of that organ/system. Grades 2 and 3 include skin, eye/nose, digestive, and/or uterine involvement, either 1 or more than 1 of them, respectively. Lx and/or BR involvement (even isolated) classifies a reaction as Grade 4, and CV and/or NS involvement (even isolated) as grade 5. In grades 4 and 5, other target organ/systems of lower grades may be affected. oFASS-3 is a simplified version, where mild corresponds to grade 1, moderate to grades 2 and 3, and severe to grades 4 and 5 of the oFASS-5 (14). FAQLQ: Food Allergy Quality of Life Questionaire (total items 29, maximum range 174); ISAC: immuno solid-phase allergen chip. Levels of IgE are measured in KU/L; levels of IgG4 are measured in mgA/L; Serum IgE against 112 allergens. Results are positive for 7 nsLTP: Ara h9, Cor a8, Jur r3, Pru p3, Art v3, Ole e7, Pla a3. None of our patients is sensitized to specific species.

## Discussion

Cluster doses in one day are safe and fast to induce tolerance to SLIT-peach® in patients with a 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 of 22 patients, with a cumulative dose of 16,442 µg (2 hours and 15 minutes duration) and a daily maintenance dose of 8 mg of Pru p3. The daily application at home proposed makes a cumulative dose of 1,440 µg 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 *et al.* (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 µg of Pru p3, this is superior compared 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, it could be 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 anaphy-

laxis. Cluster administration in one day is well tolerated. Severity score oFASS does not predict tolerance to SLIT-peach in patients with LTP-syndrome.

**Fundings**

None.

**Contributions**

ACM: conceptualization; MSZP: writing - original draft, writing - review & editing. YPP: writing - original draft. JCZ: data curation.

**Conflict of interests**

The authors declare that they have no conflict of interests.

**References**

1. Pajno GB, Fernandez-Rivas M, Arasi S, Roberts G, Akdis CA, Alvaro-Lozano M, et al. EAACI Allergen Immunotherapy Guidelines Group EAACI guidelines on allergen immunotherapy: IgE-mediated food allergy. Allergy. 2018;73(4):799-815. doi: 10.1111/all.13319.
2. Bartoll E, Nieto M, Selva B, Badillo R, Pereira G, Uixera S, et al. Validation of a Spanish version of the EuroPrevall Food Allergy Quality of Life Questionnaire-Parental Form. Allergol Immunopathol (Madr). 2018;46(1):82-6. doi: 10.1016/j.aller.2017.06.004.
3. Lei DK, Saltoun C. Allergen immunotherapy: definition, indications, and reactions. Allergy Asthma Proc. 2019;40(6):369-71. doi: 10.2500/aap.2019.40.4249.
4. Nakagome K, Nagata M. Allergen Immunotherapy in Asthma. Pathogens. 2021;10(11):1406. doi: 10.3390/pathogens10111406.
5. Vitiello G, Maltagliati L, Rossi O. New perspectives in allergen specific immunotherapy driven by big trials with house dust mite sublingual SQ® tablets. Clin Mol Allergy. 2020;18:10. doi: 10.1186/s12948-020-00124-7.
6. Schoos AM, Bullens D, Chawes BL, Costa J, De Vlieger L, Dunn-Galvin A, et al. Immunological Outcomes of Allergen-Specific Immunotherapy in Food Allergy. Front Immunol. 2020;11:568598. doi: 10.3389/fimmu.2020.568598.
7. González Pérez A, Carbonell Martínez A, Escudero Pastor AI, Navarro Garrido C, Miralles López JC. Pru p 3 oral immunotherapy efficacy, induced immunological changes and quality of life improvement in patients with LTP syndrome. Clin Transl Allergy. 2020;10:20. doi: 10.1186/s13601-020-00325-y.
8. 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. doi: 10.1111/cea.12901.
9. Jones SM, Kim EH, Nadeau KC, Nowak-Wegrzyn A, Wood RA, Sampson HA, et al. Efficacy and safety of oral immunotherapy in children aged 1-3 years with peanut allergy (the Immune Tolerance Network IMPACT trial): a randomised placebo-controlled study. Lancet. 2022;399(10322):359-71. doi: 10.1016/S0140-6736(21)02390-4.
10. Muraro A, Werfel T, Hoffmann-Sommergruber K, Roberts G, Beyer K, Bindslev-Jensen C, et al. EAACI food allergy and anaphylaxis guidelines: diagnosis and management of food allergy. Allergy. 2014;69(8):1008-25. doi: 10.1111/all.12429.
11. Pereira C, Bartolomé B, Asturias JA, Ibarrola I, Tavares B, Loureiro G, Machado D, Chieira C. Specific sublingual immunotherapy with peach LTP (Pru p 3). One year treatment: a case report. Cases J. 2009;2:6553. doi: 10.1186/1757-1626-2-6553.
12. Moura AL, Pereira C, Regateiro FS, Azevedo J, Todo Bom A, Carrapatoso I. Pru p 3 sublingual immunotherapy ultra-rush protocol is safe and clinically effective. Eur Ann Allergy Clin Immunol. 2019;51(5):206-12. doi: 10.23822/EurAnnACI.1764-1489.99.
13. 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. doi: 10.1111/j.1398-9995.2008.01921.x.
14. Fernández-Rivas M, Gómez García I, Gonzalo-Fernández A, Fuentes Ferrer M, Dölle-Bierke S, Marco-Martín G, et al. Development and validation of the food allergy severity score. Allergy. 2022;77(5):1545-1558. doi: 10.1111/all.15165.