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Evaluation of a pre-co-seasonal and a perennial schedule of a single multiallergen depigmented-polymerized subcutaneous immunotherapy in paediatric patients

Ana Martinez[a], Javier Torres[b], Ana Belen Molina[b], Candelaria Muños[c], Manuel Diaz[a], Jose Luis Corzo[c], Luis Echeverria[d], Jaime Sanchez[e], Monica Ruiz[e]

[a]*Allergy Department, Hospital Universitario Virgen de las Nieves, Granada*
[b]*Allergy Department, Hospital Materno Infantil Reina Sofía, Córdoba*
[c]*Allergy Department, Hospital Regional Universitario, Málaga*
[d]*Allergy Department, Hospital Universitario Severo Ochoa. Leganés*
[e]*Medical Affairs and Clinical Department, LETI Pharma S.L.U.*

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Abstract
Aim: Compare a pre-co-seasonal with a perennial schedule using an undiluted mixture of a depigmented-polymerized grass/*Olea europaea* immunotherapy (2,000 DPP/mL) in pediatric patients with rhinitis/rhinoconjunctivitis with or without controlled asthma.
Material and Methods: Primary objective was to determine the non-superiority of a perennial compared to a pre-co-seasonal schedule by means of Paediatric/Adolescent Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ/AdolRQLQ). Secondary objectives were Paediatric Asthma/Caregiver´s Quality of Life Questionnaire (PAQLQ/PACQLQ) Asthma Control Test (ACT), Visual Analogue Scale global assessment of allergic disease (VAS), use of resources and immunological response. All variables were compared during the pollen season (April-June) without (2015) and with (2016) immunotherapy.
Results: Forty patients were included in the study of which 29 patients were assigned to the perennial and 11 to the pre-co-seasonal schedule. During 2016 pollen season a significant improvement in the PRQLQ/AdolRQLQ, PAQLQ/AdolAQLQ, ACT and VAS score were observed both in perennial and pre-co-seasonal schedule group. No significant differences were seen between treatment schedules for PRQLQ/AdolRQLQ, PAQLQ/AdolAQLQ and ACT scores comparing both pollen seasons. A significant increase in $sIgG_4$ and reduction in the number of rescue medications used and number of patients who needed visit to any specialist was observed in both treatment schedules during 2016 pollen season. No relevant differences were found in the safety profile of any treatment schedule.
Discussion: Treatment with undiluted mixture of a depigmented-polymerized Grass/*Olea europaea* allergen immunotherapy has proven to be effective both using a perennial and a pre-co-seasonal schedule and therefore suitable for polyallergic patients.

***Corresponding author**: Monica Ruiz-Garcia, Medical Affairs and Clinical Department LETI Pharma S.L.U. Madrid, Spain. *E-mail address*: mruiz@leti.com

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Introduction

Allergic rhinitis (AR) is a chronic, aeroallergen-induced, immunoglobulin E (IgE)-mediated inflammatory disease of the upper airways that affects up to 30% of adults and up to 40% of children, and it has an impact on asthma.[1-3] It is accepted that AR has a considerable disease burden, with socioeconomic impact, negative effects on health-related quality of life, work, and school performance.[4-6] Allergen immunotherapy (AIT) is a disease-modifying and etiological treatment for IgE-mediated respiratory allergies,[7] it has proven to be effective both for sublingual (SLIT) and subcutaneous (SCIT) AIT and it is safe as well. There is a debate about the optimal regimen of AIT administration, especially with regards to pollen allergies, which have a marked seasonal component. Pre-seasonal (before the pollen season), pre-co-seasonal (before and during the pollen season), as well as, perennial (year-round) administration schedules have been proposed.[8,9] Most perennial schedules reach higher cumulative doses over time, however, this can be overcome by increasing the frequency of AIT administrations in pre-co-seasonal and pre-seasonal schedules. Pre and pre-co-seasonal schedules allow the physician to initiate immunotherapy closer to the pollen season. Not many studies have compared two different AIT treatment schedules in children, most have been performed with SLIT immunotherapy and in adults.[10,11]

Depigmented-polymerized allergen extracts (DPAEs) absorbed onto aluminium hydroxide have demonstrated their clinical efficacy in several studies conducted with different allergens and in polysensitized patients while keeping a good safety profile.[12,13] The efficacy of Depigoid® in polyallergic patients sensitized to *Cynodon* and *Olea europaea* has been previously proven in adult patients.[14] Depigoid® DUO GrassMix/*Olea europaea* (2,000 DPP/mL) is a single multiallergen DPAE indicated for patients who are polyallergic to grasses and *Olea europaea* pollens. To date, no study has compared pre-co-seasonal and perennial schedules with Depigoid® DUO.

Material and Methods

The authors conducted an observational, post-authorization, multi-center, prospective study (EPA-SP), to evaluate if a 4-month pre-co-seasonal schedule of Depigoid® DUO GrassMix/*Olea europaea* was not inferior analyzed by means of Paediatric/Adolescent Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ/AdolRQLQ), to a perennial schedule, during the following pollen season to treatment initiation. This study was conducted in Granada, Córdoba Málaga and Madrid (Spain), areas with high grass and olive pollen load, with the approval of the corresponding ethics committee and previous consent by parents or legal guardians of study participants.

Children and adolescents (aged 5 to 16 years) with moderate to severe AR or rhinoconjunctivitis following Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines,[1] due to grass and olive pollen co-sensitisation, with or without controlled asthma, were included. Co-sensitization was determined by positive Skin Prick Test (SPT) (wheal ≥ 3 mm) and positive specific IgE (sIgE ≥ 0.75 kU/L) to grass and olive pollen. Patients were assigned to a schedule depending on the month in which treatment was initiated. Those patients who initiated treatment between September and October 2015 were assigned to a perennial schedule. Conversely, those patients who initiated treatment between January and February 2016 were assigned to a pre-co-seasonal schedule. In all cases, two administrations of 0.2 and 0.3 mL at 30-min intervals constituted the *rush* build-up phase, followed by a maintenance phase of 0.5 mL, monthly in perennial schedule group for 11 months and bi-weekly in pre-co-seasonal schedule group for approximately 5 months. In both groups, a total of 13 doses of Depigoid® DUO GrassMix/*Olea europaea* were administered.

Primary effectiveness outcome was evaluated using the disease-specific quality of life questionnaire PRQLQ or AdolRQLQ, depending on the patient's age.[15] Questionnaires were administered during the pollen seasons (April–June) before (year 2015) and after (year 2016) treatment initiation. Non-inferiority between groups was calculated with a bilateral equivalence test. A difference above 0.5 points was pre-established to demonstrate clinical relevance. Secondary outcomes were Paediatric and Adolescent Asthma Quality of Life Questionnaire (PAQLQ/AdolAQLQ). If concomitant asthma was present,[16] global perception of disease improvement measured with a Visual Analogue Scale (VAS), by both the participant or legal guardian and the physician, Asthma Control Test (ACT), changes in GrassMix, *Phleum* and olive specific IgG4 (sIgG4), change in IL-10 and interferon (IFN), degree of satisfaction using Likert scale, and the use of healthcare resources were advised. Safety was recorded and adverse events were graded according to

Table 1 Baseline characteristics.

	Perennial (n = 29)	Pre-co-seasonal (n = 11)
Gender (male), *n* (%)	16 (55.2%)	10 (90.9%)
Age (median, range)	9 years (7–10)	8 years (6–9)
Place of residency:		
Urban n (%)	12 (41.4%)	5 (45.5%)
Suburban n (%)	8 (27.6%)	1 (9.1%)
Rural n (%)	9 (31.0%)	5 (45.5%)
Breastfeeding* (yes)	24 (82.8%)	5 (45.5%)
Time since diagnosis (median, range)	2 years (0–4)	2 years (0–5)
Concomitant asthma, *n* (%)	21 (72.4%)	11 (100.0%)
Skin Prick test (mm) (median, range)		
Grasses mix	6.0 (5.0–7.5)	5.5 (4.5–7.0)
Olea europaea	6.5 (5.0–8.0)	6.5 (5.5–8.0)
Specific IgE (kU/L) (median, range)		
Grasses mix	26.7 (14.0–48.6)	13.8 (5.6–15.5)
Olea europaea	33.2 (13.8–55.5)	94.9 (83.6–283.0)
No of allergen sensitizations (median, range)	3 (2–4)	3 (2–3)

*Differences between groups $p < 0.05$.

the European Academy of Allergy and Clinical Inmunology (EAACI) 2006 grading system.[17]

Results

To be taken as study subjects, 65 patients were screened. Of which only 40 patients were included. Reasons for exclusion were missing informed consent (n = 1), Forced Expiratoy Volume in the 1st second (FEV_1) < 80% (n = 1), uncontrolled asthma (n = 4), mild rhinitis/rhinoconjunctivitis without asthma (n = 1), no baseline PRQLQ/AdolRQLQ (n = 11) data and/or missing grass or olive SPT or sIgE (n = 7). Further, 29 patients were assigned to the perennial schedule and 11 patients to the pre-co-seasonal schedule. This assignment was performed depending on patients'/ parents' preferences. A difference of 0.5 between the PRQLQ values is considered clinically relevant. A standard deviation of 0.75 and a difference of 0.10 between the two means were expected. With this information and using a 5% level of significance and 80% potency, a sample of 94 patients (47 per group) was required to show the non-inferiority between schedules.

No significant differences between groups were seen at baseline except for breastfeeding, where significantly more patients were breastfed in perennial than pre-co-seasonal group (p = 0.04), Table 1.

In both groups, most of the patients (79.3% perennial schedule group and 81.8% pre-co-seasonal schedule group) had intermittent moderate-to-severe AR, and asthma was present in 72.4% in perennial schedule group and 100% in pre-co-seasonal schedule group. Furthermore, 24 patients in perennial schedule group and 10 in the pre-co-seasonal schedule group completed the treatment.

Results for primary and secondary endpoints are given as mean and SD. These results are shown in Tables 2 and 3.

Table 2 Effectiveness evaluation.

	2015 pollen season	2016 pollen season	Difference[a] (p)
PRQLQ/AdolRQLQ [mean (SD)]			
Perennial	3.77 (0.68)	2.07 (1.64)	1.70 (**<0.0001**)
Pre-co-seasonal	4.06 (0.79)	2.16 (1.40)	1.91 (**0.0006**)
Difference[b] (p)	0.29 (0.26)	0.09 (0.88)	0.20 (0.6534)
PAQLQ [mean (SD)]			
Perennial	3.39 (1.23)	4.78 (1.47)	1.29 (**0.0048**)
Pre-co-seasonal	3.47 (1.50)	5.40 (1.48)	1.78 (**0.0105**)
Difference[b] (p)	0.08 (0.90)	0.62 (0.35)	0.48 (0.4484)
ACT [mean (SD)]			
Perennial	13.7 (4.2)	18.4 (6.5)	5.05 (**0.0055**)
Pre-co-seasonal	15.1 (6.1)	21.1 (5.5)	5.00 (**0.0094**)
Difference[b] (p)	1.40 (0.45)	2.70 (0.30)	0.1 (0.9837)
VAS global perception of disease Perennial mean (SD)			
Patient	2.9 (2.4)	4.9 (3.2)	1.77 (**0.0082**)
Legal guardian	4.0 (2.4)	5.7 (3.1)	1.55 (**0.0434**)
Investigator	3.9 (1.8)	5.3 (2.8)	1.60 (**0.0325**)
Investigator (asthma patients)	4.2 (2.0)	6.0 (2.8)	2.06 (**0.0326**)
VAS global perception of disease Pre-co-seasonal mean (SD)			
Patient	2.3 (2.0)	5.3 (1.8)	2.89 (**0.0046**)
Legal guardian	3.0 (1.9)	7.1 (2.4)	3.91 (**0.0105**)
Investigator	4.2 (1.8)	6.9 (1.0)	2.62 (**0.0032**)
Investigator (asthma patients)	4.3 (2.0)	7.6 (1.4)	3.23 (**0.0050**)
$sIgG_4$ mean (SD) (kUA/L)			
GrassMix			
Perennial	0.44 (0.27)	2.11 (2.70)	1.7 (**0.004**)
Pre-co-seasonal	0.28 (0.14)	2.93 (2.71)	2.7 (**0.012**)
Phleum			
Perennial	0.23 (0.18)	1.61 (2.35)	1.4 (**0.0075**)
Pre-co-seasonal	0.15 (0.11)	2.15 (2.10)	2.0 (**0.0135**)
Olive			
Perennial	0.65 (0.75)	10.4 (7.72)	9.8 (**<0.0001**)
Pre-co-seasonal	1.05 (1.29)	14.89 (14.05)	14.6 (**0.012**)

2015: Pollen season before treatment; 2016: First pollen season after treatment initiation. PRQLQ/AdolRQLQ: Pediatric/ Adolescent Rhinoconjunctivitis quality of life questionnaire; PAQLQ: Pediatric Asthma Quality of life Questionnaire; ACT: Asthma Control Test; $sIgG_4$: specific Immunoglobulin G4. Difference[a]: 2016–2015 difference; Difference[b]: Difference between perennial and pre-co-seasonal; VAS: Visual Analogue Scale.
Results in bold p<0.05.

Changes in the PRQLQ/AdolRQLQ scores showed a significant improvement of 1.70 [1.25] in perennial schedule group ($p < 0.0001$) and 1.91 [1.28] in pre-co-seasonal schedule group ($p = 0.0006$) during 2016 pollen season. No significant differences were seen between treatment schedules for PRQLQ/AdolRQLQ comparing 2015 and 2016 pollen season (Table 2), however, there were not enough data to prove the non-inferiority of the pre-co-seasonal schedule against the perennial schedule during 2016 pollen season. Similarly, it was observed that a significant improvement in PAQLQ/AdolAQLQ of 1.29 [1.35] for perennial schedule group ($p = 0.0048$) and 1.78 [1.45] for pre-co-seasonal schedule group ($p = 0.0105$) during 2016 pollen season. ACT score results showed a significant improvement of 5.05 [7.0] for perennial schedule group ($p = 0.0055$) and of 5.0 [4.4] for pre-co-seasonal schedule group ($p = 0.0094$) during 2016 pollen season. No significant differences were found for PAQLQ/AdolAQLQ and ACT scores between treatment schedules when comparing both pollen seasons (Table 2).

Results in VAS showed a significant improvement in the global perception of the disease for both treatment schedules evaluated by the participant; 1.77 [3.2] ($p = 0.0082$) for perennial schedule group and 2.89 [2.2] ($p = 0.0046$) for pre-co-seasonal schedule group, legal guardian; 1.55 [3.4] ($p = 0.0434$) and 3.91 [3.2] ($p = 0.0105$) respectively and investigator; 1.60 [3.4] ($p = 0.0325$) and 2.62 [2.1] ($p = 0.0032$), respectively (Table 2). A significant increase in GrassMix, *Phleum*, and olive $sIgG_4$ was observed in both treatment schedules during 2016 pollen season (Table 2). No significant differences were observed for IL-10 and IFN during 2016 pollen season compared with that of 2015 pollen season or between treatment groups (data not shown).

Most patients and legal guardians were satisfied or very satisfied (Likert scale) regarding improvement in symptoms and reduction in use of medication, route of administration, and with the treatment itself for both treatment schedules and without differences between treatment schedules (data not shown).

The pharmacoeconomic impact of these two treatment schedules was also analyzed (Table 3). During 2015 pollen season, all patients required rescue medication and in both treatment groups patients had loss of school days (Table 3). Visits to an Allergy Specialist and/or Emergency Department due to the allergic disease were significantly higher (Table 3) in the pre-co-seasonal schedule group. During 2016 pollen season, the number of rescue medications used was reduced for both treatment groups (Table 3).

The use of rescue medication was only significantly reduced in the perennial schedule group; 24% ($p = 0.006$) of patients in this group did not require any rescue medication during 2016 pollen season. During 2016 pollen season, the number of patients who needed visit to any specialist, including Emergency Department was significantly reduced

Table 3 Pharmacoeconomic evaluation.

	2015 pollen season	2016 pollen season	Difference[a] (p)
Visits to allergy specialist and/or emergency department, n (%)			
Perennial	14 (48.3%)	4 (13.8%)	**0.017**
Pre-co-seasonal	10 (90.9%)	1 (9.1%)	**<0.0001**
Difference[b] (p)	0.0274	1.0000	-
School days lost, n (%)			
Perennial	1 (3.6%)	2 (7.1%)	**0.223**
Pre-co-seasonal	9 (81.8%)	0	**0.015**
Difference[b] (p)	<0.0001	1.000	-
Use of rescue medication, n (%)			
Perennial	29 (100%)	22 (75.9%)	0.006
Pre-co-seasonal	11 (100%)	11 (100%)	1.000
Oral antihistamines, n (%)			
Perennial	26 (89.7%)	16 (72.7%)	0.002
Pre-co-seasonal	11 (100%)	7 (63.6%)	0.038
Difference[b] (p)	0.55	0.70	-
Nasal steroids, n (%)			
Perennial	15 (51.7%)	9 (40.9%)	0.031
Pre-co-seasonal	7 (63.6%)	3 (27.3%)	0.104
Difference[b] (p)	0.72	0.70	-
Other treatment, n (%)			
Perennial	28 (96.6%)	18 (81.8%)	0.001
Pre-co-seasonal	10 (90.9%)	10 (90.9%)	1.000
Difference[b] (p)	0.48	0.64	-

2015: Pollen season before treatment; 2016: First pollen season after treatment initiation.
Difference[a]: Difference between pollen seasons.
Difference[b]: Difference between perennial and pre-co-seasonal.
Results in bold $p<0.05$

in 34.5% (p = 0.017) of patients in the perennial schedule and 81.8% (p < 0.0001) of patients in pre-co-seasonal schedule who required these visits in 2015 pollen season. None of the patients in the pre-co-seasonal schedule had loss of school days in 2016 pollen season compared with that of 9 (81.8%) in 2015 pollen season and this was statistically significant (p = 0.015). Two (7.1%) patients had loss of school days in the perennial schedule in 2016 pollen season compared with that of 1 (3.6%) during 2015 pollen season (Table 3).

No relevant differences were found in the safety profiles of any treatment schedule. Two patients had a local reaction and one patient had a Grade I (EAACI classification) systemic reaction (mild wheezing) in the perennial schedule. Two patients had four systemic reactions: one Grade 0 (pruritus) and three Grade 1 (lips edema, rhinorrhea, and mild wheezing) in the pre-co-seasonal schedule.

Discussion

In this article, an improvement in disease-related quality of life was observed one pollen season after treatment initiation, similar to findings in different clinical trials[14,18,19] and observational studies.[20]

These results show that both perennial and bi-weekly pre-co-seasonal schedules, both reaching almost the same cumulative dose at pollen season are effective, thus, stressing the importance of the cumulative dose a patient receives before the pollen season irrespective of treatment schedule.

The main limitations of this study are: (i) the small number of participants included, which is probably responsible for not being able to demonstrate non-inferiority between treatment schedules, and (ii) the lack of control group; however, baseline data were collected during the previous pollen season (without AIT treatment) which allowed intragroup comparison.

Interestingly both treatment schedules showed a pharmacoeconomic benefit with reduction in rescue medication, use of clinical resources, and very importantly in days of school lost, being this remarkably improved in the pre-co-seasonal schedule group.

All these results show that both schedules are effective in improving patients' quality of life, better control of asthma, and reducing the economic impact of respiratory allergic diseases due to grass and olive pollen, which are two of the most prevalent aeroallergens in Spain. Regarding the satisfaction of patients and legal guardians, the bi-weekly treatment administration was no different to monthly treatment administration, however, similar studies in adult participants should be performed in order to determine a possible impact in long-term treatment adherence.

In conclusion, this artice has demonstrated, for the first time to our knowledge, the safety and effectiveness of two different treatment schedules for a dual allergy using a single multi-allergen SCIT.

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