

Efficacy and Quality of Life With Once-Daily Sublingual Immunotherapy With Grasses Plus Olive Pollen Extract Without Updosing

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■ Abstract

Objective: The purpose of this randomized, double-blind, placebo-controlled study was to evaluate the clinical efficacy and tolerance of once-daily sublingual immunotherapy without updosing. Reduction in symptoms and medication use was the primary endpoint.

Methods: One hundred five patients with rhinitis and/or asthma due to grass and olive sensitization were randomized to be treated with placebo or active sublingual immunotherapy with the SLITone grass mix plus olive pollen extract for 6 months before the 2005 pollen season. Patients recorded symptoms and medication intake for 8 weeks during the pollen seasons in 2004 (n = 37) and 2005 (n = 85).

Results: Allergic symptoms were significantly decreased in the active immunotherapy group ($P = .004$) but not in the placebo group. There were no differences in scores between groups during the 2005 pollen season. Subjective assessments on a visual analog scale and a quality-of-life questionnaire indicated an improvement in actively treated patients with significant differences in both symptoms and medication use ($P = .006$). The rate of systemic adverse reactions was comparable in the 2 groups. No anaphylactic or severe adverse reactions were reported. Local adverse reactions, which were more common in the active immunotherapy group, were mostly immediate, were limited to the lips and mouth, and did not require treatment.

Conclusion: Once-daily sublingual immunotherapy without updosing was well tolerated. The actively treated patients showed a significant reduction in symptom and medication scores and an improvement in their quality of life although there were no significant differences between the groups probably due to the low allergen season in which the study was evaluated.

Key words: *Olea* species. Grasses. Sublingual immunotherapy. Rhinitis. Allergens. Clinical efficacy. Tolerance.

■ Resumen

Objetivo: El objetivo del presente estudio randomizado, doble ciego controlado con placebo ha sido evaluar la eficacia clínica y tolerancia de la inmunoterapia sublingual diaria sin fase de inicio. La variable principal de evaluación consistió en la reducción de síntomas y uso de medicación.

Métodos: Se aleatorizaron 105 pacientes con rinitis y/o asma por sensibilización a gramíneas y a olivo para recibir tratamiento placebo o activo (SLITone mezcla de gramíneas y olivo) durante los 6 meses anteriores a la época de polinización de 2005. Los pacientes registraron síntomas y medicación durante 8 semanas en la estación polínica de 2004 (n = 37) y 2005 (n = 85).

Resultados: Los síntomas alérgicos disminuyeron significativamente en el grupo activo ($P = .004$) y no en el placebo. No hubo diferencias en la puntuación de los grupos durante la estación polínica de 2005. La evaluación subjetiva de la enfermedad en la escala visual analógica y de la calidad de vida indicaron una mejoría significativa en los pacientes que recibieron tratamiento activo ($P = .006$ en ambos parámetros). La tasa de reacciones adversas sistémicas fue similar en los dos grupos. No se registraron reacciones anafilácticas ni

acontecimientos adversos graves. Las reacciones locales adversas fueron más frecuentes en el grupo activo siendo la mayoría inmediatas y limitadas a labios y boca, y no requirieron tratamiento.

Conclusión: La administración diaria de SLIT sin fase de inicio fue bien tolerada. Los pacientes tratados activamente presentaron una reducción significativa en la puntuación de síntomas y uso de medicación y una mejora en su calidad de vida aunque sin diferencias significativas con el grupo control, debido probablemente a la baja presión alérgica en la estación en la que se realizó el estudio.

Palabras clave: *Olea* especies. Gramíneas. Inmunoterapia sublingual. Rinitis. Alérgenos. Eficacia clínica. Tolerancia.

Introduction

Epidemiologic studies have revealed considerable escalation of allergic diseases in developed countries in recent years [1]. The prevalence of respiratory allergic diseases varies in different European countries [2]. Twenty-three percent of adults in Europe suffer from allergic rhinitis, which is the most frequent allergic disease [3,4] and the most common cause for consultation for allergy in our region. Allergic rhinitis, although not a severe or life-threatening condition, is usually the cause of evident deterioration in quality of life and gives rise to a considerable amount of sick leave from work or school [5]. Rhinitis frequently presents itself in association with asthma, a comorbidity that affects up to 78% of asthmatic individuals [6].

The ability of olive pollen to induce rhinitis and/or asthma in exposed populations through an immunoglobulin-E-mediated mechanism is widely documented in the European Mediterranean areas [7-10]. Although the exposure period of patients to that allergen is short (about 6 weeks), its ability to produce severe symptoms in sensitized patients is notable [11].

Treatment options in respiratory allergic disease are allergen avoidance, which in some cases might be extremely difficult, symptomatic treatment with appropriate drugs, and the etiologic treatment by way of specific immunotherapy. In 1998, the World Health Organization underlined the clinical benefit of using specific immunotherapy [12], which consists of reducing symptoms and use of medication, preventing new sensitizations [13], and interrupting allergy progression from rhinitis to asthma [14]. The sublingual route for administration of immunotherapy has been proven in a number of double-blind placebo-controlled studies to be clinically efficacious and have a long-term effect as well as excellent tolerability [15-19]. Two clinical trials have been performed with a grass extract similar to the one used in the present study [16,20]. In both trials a 5-species assortment was used (*Dactylis glomerata*, *Festuca pratensis*, *Lolium perenne*, *Phleum pratense*, *Poa pratensis*). The treatment required the administration of several initiation vials before reaching a maintenance dose. In the present study, the treatment used was SLITone (ALK-Abelló SA, Madrid, Spain), which incorporates some modifications from the treatment of the 2 previous trials. Firstly, its composition includes extracts of 2 important species in our region, *Secale cereale* and *Olea europaea*. Secondly, its pharmaceutical presentation starts directly with single daily dose maintenance vials, without a build-up phase. Considering these differences,

and with the objective of assessing the efficacy and safety of the 6-grasses-plus-olive extract administered sublingually, we set up a multicenter double-blind placebo-controlled clinical trial.

Material and Methods

Patients and Design

Patients aged 14 to 55 years with at least 1 year of clinical history of moderate-severe seasonal allergic rhinitis to grasses and *O europaea* pollen, with or without asthma symptoms, were recruited. Positive skin prick tests (mean diameter of wheal, ≥ 3 mm with a diagnostic prick test; ALK-Abelló SA, Madrid, Spain) to grass mix extracts and *O europaea* were required. Patients fulfilling any of the following criteria were excluded: perennial rhinitis or asthma, clinically relevant sensitization to *Dermatophagoides pteronyssinus*, *Alternaria alternata*, cat and/or dog dander, treatment with grass or *O europaea* allergenic vaccines within the 2 years previous to study initiation, absolute or relative contraindications to immunotherapy [21], or any other condition that, under the investigators criteria, could compromise the patient's safety. Informed consent was obtained from participant patients.

The study was designed as a randomized, double-blind placebo-controlled, parallel group clinical trial. It was performed on 3 sites in Spain (Cordoba, Madrid, and Plasencia) that usually have high densities of grass and olive pollens and high prevalences of patients allergic to these pollens. Patients were randomly allocated to either active sublingual immunotherapy (mixed-grass + olive) or placebo. Randomization was performed in blocks and a history of concomitant asthma was a criterion for stratification.

Immunotherapy

The extract was biologically standardized by major allergens (grass Group 5 and Ole e 1) and quantified in micrograms. Daily dose contained 2 μ g of grass Group 5 and 3 μ g of *O europaea* Ole e 1. Placebo was similar in taste and appearance. Immunotherapy was administered daily, by sublingual route, following the same schedule for all patients.

Immunotherapy was initiated directly by the patients with the administration of single-dose containers, each one with an extractable volume of 0.2 mL. The first dose was administered at the clinic and the following ones at home. The immunotherapy course spanned approximately 10 months, beginning in September 2004 and ending in July 2005. The administration continued during the pollen season (coseasonal immunotherapy).

In order to assess immunotherapy compliance, each patient received an administration follow-up diary card, where he/she recorded each administered dose as well as any incidents related to the treatment or to his/her allergic disease or any other concomitant disease. The investigators reviewed this card at every control visit and compliance of each patient was assessed until the end of the study or drop-out/withdrawal.

Tolerance

Adverse events were recorded in detail throughout the study. They were classified by the investigators according to severity and relation to treatment (not assessable, unlikely, possible, likely, certain) [22]. In case treatment was needed to control the event, this was also recorded.

Symptom and Medication Score

During the spring of 2004, before the start of immunotherapy, and during the spring of 2005, during coseasonal administration of SLITone, allergic symptoms and antiallergic medication were recorded daily during 8 consecutive weeks coinciding with the grass and olive pollen seasons of both years. Symptoms measured were nasal (itching, sneezing, nose clogging, rhinorrhea); ocular (ocular discomfort, itching, redness), and bronchial (cough, wheezing, shortness of breath). Symptoms were scored according to the following scale: 0, absent; 1, mild: not causing discomfort or interfering with daily activities; 2, moderate: causing discomfort but not interfering with daily activities or sleep; and 3, severe: causing intense discomfort and interfering with daily activities and/or sleep.

Rescue medication was prescribed by each investigator and administered to the patients for as-needed use to control their allergic symptoms: for rhinitis, nasal and oral antihistamines and oral corticosteroids; for conjunctivitis, ocular and oral antihistamines and oral corticosteroids; and for asthma, short- and long-acting β_2 -agonists and inhaled and oral corticosteroids. Medication use was scored as follows: any use of antihistamines and/or a short-acting β_2 -agonist, 1 point; use of a long-acting β_2 -agonist plus inhaled corticosteroids, 3, 6, or 9 points, respectively for low (<200 μg), moderate (200-500 μg), or high doses (>500) of budesonide or the equivalent); oral corticosteroids, 3 points.

After completion of the diary cards in both pollen seasons (years 2004 and 2005), patients graded the overall severity of their disease on a 10-cm visual analog scale (VAS) ranging from free of symptoms to the most intense symptoms possible.

Pollen Counts

Grass and olive pollen counts in the spring of 2005 were very low throughout Spain, with average cumulative counts of 5800 olive pollen grains and 1200 grass pollen grains per cubic meter through the season during which patients evaluated their symptoms and medication scores (May and June). The 2004 pollen season, although lower than normal seasons, showed higher pollen counts for grass pollens than in 2005, averaging an accumulated value of 5700 and 2600 pollen grains per cubic meter for olive and grasses, respectively.

Rhinitis Quality-of-Life Questionnaire

Patients completed a validated rhinitis-specific, self-administered quality-of-life questionnaire during the 2004 and 2005 pollen seasons [23,24].

Statistical Analysis

The primary endpoint was reduction in symptom and medication scores and this was analyzed by nonparametric tests (Mann-Whitney for intergroup comparisons and Wilcoxon for intragroup comparisons) on all patients with valid data. Symptoms as well as medication were analyzed both individually and grouped by organ (nasal, ocular, bronchial and total). In addition intergroup differences in the total score for every variable were assessed at baseline (pollen season 2004) and at the end of the study (pollen season 2005). Likewise, intragroup changes between the seasons were analyzed.

P values less than .05 were considered statistically significant and 2-sided tests were used. Adverse events were assessed on all randomized patients. The frequency of adverse events was calculated by patient and by administered dose. All adverse events were classified according to the Medical Dictionary for Regulatory Activities and frequencies of adverse events were compared with the Fisher exact test (bilateral).

Results

Patients and Therapies

A total of 105 patients were randomized; 100 received treatment, 51 active and 49 placebo. Twenty patients left the study: 11 in the active therapy group and 9 in the placebo group (figure). Five dropped out during the run-in and 15 once therapy had begun. In 14 out of the 20 withdrawals, there was no relation to therapy, but in 6 patients, all in active therapy group, the withdrawals were due to an adverse event (5 systemic and 1 local reaction). Patient characteristics are shown in Table 1.

Immunotherapy was administered for a mean duration of 248 days, including a pre-seasonal treatment period of 207 days. Duration of treatment was similar in the 2 treatment groups. Compliance was 92.2% for all patients and 94.1% for patients who completed the sublingual immunotherapy course (without differences between the groups).

Table 1. Patient Characteristics*

	Placebo	Active Therapy	Total
No. of patients	53	52	105
Age, mean (SD), y	26.0 (7.78)	28.6 (9.88)	27.3 (8.93)
Sex			
Male	30 (56.6)	28 (53.8)	58 (55.2)
Female	23 (43.4)	24 (46.2)	47 (44.8)
Duration of rhinitis, mean (SD), mo	84.2 (81.7)	79.1 (70.5)	81.6 (76.0)
Rhinitis			
Intermittent	25 (47.2)	33 (63.5)	58 (55.2)
Persistent	28 (52.8)	19 (36.5)	47 (44.8)
Conjunctivitis			
Absent	3 (5.7)	3 (5.8)	6 (5.7)
Low	18 (34.0)	21 (40.4)	39 (37.1)
Moderate	27 (50.9)	23 (44.2)	50 (47.6)
Severe	5 (9.4)	5 (9.6)	10 (9.5)
Asthma			
Absent	20 (37.7)	21 (40.4)	41 (39.0)
Low intermittent	12 (22.6)	11 (21.2)	23 (21.9)
Low persistent	8 (15.1)	7 (13.5)	15 (14.3)
Moderate persistent	13 (24.5)	13 (25.0)	26 (24.8)

* Data are number (%), unless otherwise indicated to be mean (SD).

Table 2. Adverse Reactions in the Active Treatment and Placebo Groups*

	AR		LR		SR	
	Patients With AR, No. (%)	Adverse Events	Patients With LR, No. (%)	Adverse Events	Patients With SR, No. (%)	Adverse Events
Active, n = 51	34 (66.7)	106	33 (64.7)	92	6 (11.8)	14
Placebo, n = 49	12 (24.5)	24	8 (16.3)	14	6 (12.2)	10

*AR indicates adverse reaction; LR, local reaction; SR, systemic reaction.

Tolerance

A total of 681 adverse events were reported by 92 patients. One hundred thirty events in 46 patients were related to treatment: 106 adverse events in 34 patients (66.7%) in the active immunotherapy group and 24 reactions in 12 patients (24.5%) in the placebo group (Table 2). Most systemic and local adverse reactions appeared immediately, were of short duration, and resolved spontaneously without sequelae.

All 24 systemic reactions were mild and only 7 of them required medical treatment. The most frequent clinical manifestations were similar to the patient's own allergic symptoms: conjunctivitis, rhinitis, and mild asthma. There was 1 report of urticaria in which

medical treatment was not necessary. Neither anaphylactic shock nor severe adverse reactions were observed. The rate of systemic reactions was similar for both groups at 12%.

The most frequent local reactions were apthae, itching and/or irritation of the mouth and/or tongue, ear pruritus, and throat itching. Local reactions were more frequent in the active therapy group than in the placebo group (0.11% of doses in 16% of the patients in the placebo group vs 0.76% of the doses in 65% of the patients in the active group, $P < .0001$) (Table 2).

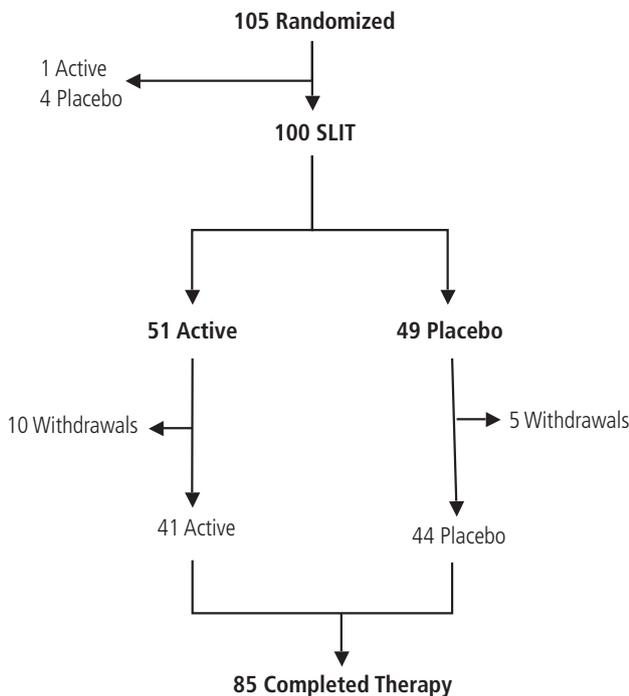
There was a single serious adverse event unrelated to treatment: digestive hemorrhage due to *Helicobacter pylori*, for which hospitalization was required. Local adverse events were more frequent during the first administered doses.

Table 3. Evolution of Symptom and Medication Scores: 2004 vs 2005*

	Placebo			Active Treatment		
	2004	2005	<i>P</i> †	2004	2005	<i>P</i> †
	Mean (SD)	Mean (SD)		Mean (SD)	Mean (SD)	
Total symptoms						
Pulmonary	0.28 (0.35)	0.14 (0.22)	.1545	0.30 (0.43)	0.16 (0.21)	.0166‡
Ocular	0.64 (0.50)	0.46 (0.31)	.1401	0.89 (0.63)	0.48 (0.39)	.0092‡
Nasal	0.74 (0.44)	0.56 (0.41)	.2933	0.88 (0.53)	0.55 (0.35)	.0076‡
Total	0.56 (0.32)	0.39 (0.29)	.1395	0.67 (0.43)	0.40 (0.21)	.0045‡
Medication						
Pulmonary	1.20 (1.89)	0.64 (1.41)	.2626	1.10 (2.72)	0.73 (1.63)	.9528
Ocular	0.62 (0.61)	0.42 (0.46)	.2804	0.70 (0.64)	0.49 (0.50)	.0596
Nasal	0.59 (0.55)	0.35 (0.36)	.0467‡	0.64 (0.45)	0.46 (0.50)	.1671
Total	2.41 (2.49)	1.41 (1.48)	.1182	2.44 (3.13)	1.68 (2.16)	.5509
Symptoms and Medication						
Pulmonary	0.88 (1.27)	0.46 (0.85)	.1093	0.85 (1.61)	0.52 (0.92)	.6100
Ocular	0.95 (0.67)	0.67 (0.45)	.0782	1.24 (0.81)	0.73 (0.61)	.0045‡
Nasal	1.04 (0.59)	0.74 (0.50)	.1240	1.20 (0.63)	0.78 (0.52)	.0199‡
Total	1.76 (1.50)	1.10 (0.94)	.0884	1.89 (1.78)	1.23 (1.14)	.1556

* All data are mean (SD).

† Wilcoxon rank sum test between 2004 and 2005. ‡ Significant difference.



Flowchart, randomized double-blind placebo-controlled trial of sublingual immunotherapy (grasses + olive pollen), SLITone (ALK-Abelló SA, Madrid, Spain). SLIT indicates sublingual immunotherapy.

Symptom, Medication, VAS and Quality-of-Life Scores

A total of 85 patients filled in the diary cards in 2005 and 37 of them also in 2004. Forty-one patients were in the active therapy group and 44 in the placebo group in 2005, and 19 were in the active group and 18 in the placebo group in 2004.

In general, few symptoms were observed. In 2005, patients recorded symptoms classified as severe only on 6% of recording days, and for 30% of the evaluated period they were free of symptoms. The use of medication was also low and took place on only 40% of recording days. Differences between active therapy and placebo groups did not reach statistical significance either in 2004 or 2005. Significant changes were observed in the intragroup analysis (2004 vs 2005) in the active group for pulmonary symptoms ($P = .016$), ocular symptoms ($P = .009$), nasal symptoms ($P = .008$), and overall symptoms ($P = .004$). In the placebo group, there was a decrease in the use of nasal medication ($P = .047$). The combined score of symptoms plus medication showed a significant and favorable evolution in nasal ($P = .020$) and ocular ($P = .004$) symptoms in the active immunotherapy group (Table 3).

In the active immunotherapy group ($n = 15$) the VAS assessment of overall disease progression changed from 54.3 in 2004 to 35.5 in 2005 ($P = .006$), whereas in the placebo group ($n = 13$) the VAS score changed from 53.3 in 2004 to 39.6 in 2005 ($P = .184$).

Rhinitis quality of life questionnaires were completed by 23 patients at baseline during the 2004 pollen season and also

during the 2005 season. The active immunotherapy group ($n = 13$) improved in all domains (activities, sleep, general symptoms, practical problems, nasal symptoms, and emotional situation) with a change in the overall score from a mean of 2.67 in 2004 to 1.25 in 2005 ($P = .006$). In the placebo group ($n = 10$), the overall score went from 2.81 in 2004 to 2.37 in 2005 ($P = .260$). There were no significant differences between groups in the 2005 season.

Discussion

The study was intended to have a baseline evaluation in the 2004 pollen season and a post-treatment evaluation after the 2005 season with the aim of assessing the decrease in symptoms and medication use after sublingual immunotherapy. For practical reasons only 37 subjects were enrolled before the 2004 season. The rest of the patients were enrolled after the 2004 pollen season and thus were only evaluated in the 2005 season. Although patients were selected according to the same inclusion and exclusion criteria, the analysis of these 2 groups revealed a significant difference in the severity of rhinitis: the subjects enrolled after the 2004 season had more severe symptoms than those enrolled for the 2004 season. We do not consider that this difference has an important impact on the results of the study because the analyses performed were for paired samples, but it limits the intragroup analysis to only those patients who had valid data in both seasons.

The results of the present study indicate that sublingual immunotherapy with a mixture of grass and olive pollen extracts is well tolerated when administered straight from maintenance dose. These results confirm those obtained from a previous multicenter study performed without up dosing [25].

After an 8 to 10 month course of sublingual immunotherapy, the change in patients' scoring by intragroup analysis of symptoms, use-of-medication scores, VAS and quality-of-life scores clearly indicated a significant improvement for patients in the active group. No changes are seen in the placebo group.

A direct interpretation of quality of life data in relation to clinical effect may however be difficult with some questionnaires. Guyatt and Jaescheke [26] have stressed the need for a demonstration of the clinical relevance of quality of life outcome measures and they have proposed that a change in score of 0.5 is the smallest clinically significant one in the questionnaires of Juniper and colleagues [23,24] that are used in many clinical studies on respiratory allergic diseases. In this study, actively treated patients demonstrate a clinically significant improvement in quality of life with rhinitis over time of 1.42.

This study was unable to demonstrate significant differences between active and placebo groups in any of the studied clinical parameters using the intergroup comparison after the 2005 pollen season. The low pollen level during the study seasons (the lowest for the last 10 years) might have influenced the lack of statistical significance. Low pollen levels reduced the allergic manifestations of patients in both groups, and further analysis demonstrated a correlation between symptoms, medication, and pollen counts (data not shown). The small changes seen might also have been more evident with a larger study sample,

adequately powered to demonstrate even small changes under circumstances with low allergenic pressure. Nevertheless, the rhinitis quality-of-life data indicate that this sublingual immunotherapy may still have an important positive impact on many patients [26].

Acknowledgments

The authors would like to thank the coinvestigators and also other persons directly involved in the development of the study for their excellent work: Isabel Ojeda, Rosa M García Carbonell, Vanesa Herrero Martínez, Eduardo Almeda Llamas, Pedro M Cosmes, Ana C Gil Adrados, Marta Cid, and Begoña Gandarias.

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