

Double-blind, placebo-controlled study with a modified therapeutic vaccine of *Salsola kali* (Russian thistle) administered through use of a cluster schedule

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Background: The inhalation of *Salsola kali* pollen is a common cause of respiratory diseases in Europe and North America.

Objective: To evaluate the efficacy and safety of a depigmented and glutaraldehyde-polymerized therapeutic vaccine of *S kali*.

Methods: The trial was randomized, double-blind, and placebo-controlled using a rush protocol in the build-up phase. Sixty patients with rhinoconjunctivitis (19 also had mild asthma) were randomly allocated to receive either active treatment (polymerized extract) or placebo. The final distribution was 41 patients in the active and 19 in the placebo group. Side effects were registered. Symptom and medication scores and the number of days free of symptoms during the pollen season were assessed to evaluate the clinical efficacy. A Rhinoconjunctivitis Quality of Life Questionnaire was completed in the previous pollen season (before treatment) and during the pollen season 1 year later (in the trial). Dose-response skin tests were performed at baseline and at the end of the trial.

Results: There was a significant difference ($P < .05$) in symptom and medication scores between both groups during the pollen season, with the active group the one that had fewer symptoms and lower intake of medication. The number of days without symptoms was higher in the active group ($P < .05$). This group also had a significant improvement in the Rhinoconjunctivitis Quality of Life Questionnaire and a reduction in skin sensitivity. No moderate or severe systemic reactions were registered.

Conclusion: Immunotherapy with this modified vaccine of *S kali* pollen is safe and efficacious to treat patients clinically sensitive to this pollen.

Clinical implications: Patients allergic to *S kali* (Russian thistle) can be successfully treated with immunotherapy to improve symptoms of allergic rhinitis and asthma, reduce medication use, and improve quality of life parameters. (J Allergy Clin Immunol 2006;117:810-6.)

Key words: *Salsola kali*, allergic rhinitis and asthma, allergens, immunotherapy, Zaragoza

The botanical family Chaenopodiaceae contains several species with allergological importance, such as *Chenopodium album* and *Salsola kali*. These 2 species are responsible of allergic sensitization in Europe and North America.¹ The genus *Salsola* is one of the better known genera of the Chaenopodiaceae family, and several species have been described, including *Salsola pestifer*, *Salsola vermiculata*, and *Salsola oppositifolia*. One of the better known species is *S kali* (Russian thistle). *S kali* is a typical plant of salty soils, where rainfall is not abundant.² It is a summer-flowering, annual weed that, as a mature plant, forms spherical bushes abundant in several arid regions of the United States and central Australia. In the United States, *Salsola* spp are found along the coast from the Northeast to the West.³ In Europe, it is also very common in coastal areas from the Baltic Sea to the Mediterranean coast.

In 1933, Lomson and Watry⁴ described the first cases of sensitization to this pollen in Arizona. Shafiee et al⁵ described 9 patients with hypersensitivity to pollen of *Salsola* spp who showed positive skin prick tests (SPTs) to Russian thistle and detectable levels of specific IgE. Studies by Gómez et al⁶ in Texas, Würtzen et al,⁷ and Shaffie et al⁸ have also attempted the characterization of *S kali* allergens. An important allergen of *S kali* has been described recently. This allergen, Sal k 1, was characterized by using sera from patients from the Zaragoza area.⁹

In some regions of Spain, more than 30% to 40% of the patients with allergy are allergic to this pollen and exhibit a positive SPTs and symptoms in late summer on exposure.^{5,10,14} Significant cross-reactivity has also been described between *Salsola*, *Chenopodium* spp,¹¹ and *Mercurialis annua*.¹²

The efficacy of immunotherapy with *S kali* is not well documented in peer-reviewed journals. A PhD thesis by de la Hoz¹³ supports the clinical benefit of this treatment. Recently an article was published on the safety of a physically modified extract (adsorbed to alum).¹⁴ The objective of this study was to evaluate the clinical efficacy and safety of a vaccine containing a chemically modified (depigmented and glutaraldehyde polymerized) extract of *S kali* in a group of patients sensitized to this pollen.

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Abbreviations used

AUC: Area under the curve

HEP: Histamine Equivalent Prick test units

RQLQ: Rhinoconjunctivitis Quality of Life Questionnaire

SPT: Skin prick test

METHODS

Patient population

Patients were recruited from the outpatient clinic of the Allergy Unit of the University Hospital “Lozano Blesa” in Zaragoza, Spain. Patients were selected consecutively as they attended the Allergy Service. All were tested with standardized extracts of the following allergens: *Phleum pratense*, *Cynodon dactylon*, *Phragmites communis*, *Olea europaea*, *Plantago lanceolata*, *S kali*, *C album*, *Artemisia vulgaris*, *Parietaria judaica*, *Alternaria alternata*, *Cladosporium herbarum*, *Aspergillus fumigatus*, *Dermatophagoides pteronyssinus*, and dog and cat epithelium. SPTs were performed according with international recommendations.¹⁵ The study was authorized by the Ethics Committee of the Hospital “Lozano Blesa” and the Spanish Health Authorities (Agencia Española del Medicamento).

The patients had to meet the following inclusion criteria: positive clinical history of allergy to *S kali* pollen during the summer, positive SPT (wheal ≥ 7 mm²) with a standardized *S kali* extract containing 100 Histamine Equivalent Prick test units (HEP)/mL (Laboratorios LETI, SL, Madrid, Spain), and a positive specific IgE determination (>0.7 kU/mL) to *S kali* (Pharmacia Diagnostics AB, Uppsala, Sweden). The following exclusion criteria were used: sensitization to molds, mites, and other pollens, excluding *C album*; immunotherapy during the last 4 years; and any contraindication for the use of immunotherapy.¹⁶ All patients gave their witnessed written consent before their participation in the study.

After a careful selection, 63 patients (age range, 18-50 years; mean, 33 years) entered the study. These patients were randomly allocated to receive either active treatment or placebo. All patients were diagnosed with allergic rhinoconjunctivitis with or without asthma. Three patients dropped out of the study (2 in the active and 1 in the placebo group). Dropouts were not a result of adverse reactions, and all 3 dropped out before the pollen season. The final distribution was 41 patients in the active and 19 in the placebo group. Thirteen patients in the active and 6 in the placebo group had mild asthma. The diagnosis and classification of asthma was made according to the Global Initiative for Asthma (<http://www.ginasthma.org>). All patients were classified as having mild disease. Patients could abandon the study at any time.

Allergen extracts and immunotherapy schedule

The depigmented and glutaraldehyde polymerized extract of *S kali* was prepared and standardized following previously published methods¹⁷⁻¹⁹ and absorbed onto aluminium hydroxide. The modified vaccines and placebo were supplied by Laboratorios LETI, SL. The allergenicity of the extracts was established by determining the 50% IgE inhibition point using the in-house reference preparation and a serum pool of individuals allergic to *S kali*, in accordance with the recommendations of the European Pharmacopoeia.²⁰ The figures were 221 ng for the native and 2.34 μ g for the modified extract. The 50% IgG inhibition points were measured by ELISA to determine vaccine immunogenicity, using the same serum pool; 11 ng was needed of the native and 88 ng of the modified extract. Excipients were sodium chloride, phenol, and aluminium hydroxide.

Two consecutively numbered vials containing placebo or the modified *S kali* extract were prepared (Laboratorios LETI, SL). The placebo contained the identical solution as the experimental product, but without active ingredients; the presentation and dosage schedules were identical. Vial 1 of the active treatment contained 45 μ g freeze-dried lyophilized extract per mL (287.9 protein nitrogen units [PNU]/mL). Vial 2 contained 450 μ g (2879 PNU/mL). Each patient received 18 injections in 14 sessions. The native extract of *S kali* contained 19% of Sal k 1/mg of freeze dried material before polymerization.

The trial medication was administered subcutaneously on the extensor surfaces of the upper arms. All patients started immunotherapy during month of October 2001. The following cluster build-up schedule was used: vial 1 was administered in 3 doses (0.1, 0.25, and 0.5 mL) injected in alternative arms during the first day at intervals of 15 to 20 minutes; vial 2 was started 1 week later using the same cluster scheme as for vial 1. The next administration followed 1 month later. All patients received a total of 12 maintenance doses of 0.5 mL (1 injection/mo). The cumulative dose of Sal k 1 during the trial was 597.65 μ g.

Pollen counts

Daily pollen counts, kindly provided by the Aerobiology Committee of the Spanish Society of Allergy and Clinical Immunology, were established by using a Burkard volumetric spore-trap (Burkard Manufacturing Co, Rockmansword, Herst, United Kingdom) and expressed as pollen grains per m³. The pollen season was defined as the period of 2002 having 90% of the total yearly Chenopodiaceae/Amaranthaceae pollen grains, starting August 15 and ending September 16.

Efficacy and safety measurements

Diary cards and symptom and medication scores. The primary endpoint of the study was the assessment of symptom scores. All patients recorded daily symptom scores during the pollen season, including nose, eyes, and lung symptoms. Nose (sneeze, blockage, and running), eye (itching, redness, and swelling) and chest symptoms (breathlessness, wheeze, chest tightness, and cough) were scored on a scale ranging from 0 to 3 (0 = none; 1 = slight, the symptom is clearly present but is not troublesome; 2 = moderate, the symptom is present, it is troublesome, but it not disabling or insufferable; and 3 = severe, the symptom is severe, disabling, and/or insufferable). The daily total symptom score was expressed as the sum of all individual scores related to eye, nose, and lungs. The medication use was recorded on diary cards, as previously described,²¹ with slight modifications. Briefly, 1 tablet of antihistamine (Loratidine; Schering-Plough, Kenilworth, NJ), 1 puff of inhaled bronchial steroids (Budesonide; AstraZeneca, Edinburgh, United Kingdom), or 1 puff of a β_2 -agonist received 1 point; 1 puff of nasal steroids received 0.75 points; and 1 puff of nasal antihistamine (Azelastine; Viartis, Hamburg, Germany) received 0.25 points. Oral steroids (prednisolone) was contemplated only for severe exacerbations and ascribed a value of 1 point/mg.

Dose-response SPTs. Patients were skin prick tested during the month of October, outside of the pollen seasons, at baseline and after 12 months of treatment. The SPTs were conducted in duplicate on the volar surface of the forearm using concentrations of 1, 0.1, 0.01, and 0.001 mg freeze-dried standardized *S kali* extract per mL (Laboratorios LETI, SL). The maximum concentration (1 mg/mL) had a biological potency of 100 HEP/mL. The same batch of native, unmodified allergen extract was used throughout the trial. The extract was supplied freeze-dried and vacuum closed to be reconstituted just before use. Histamine HCl 10 mg/mL and a glycerinated saline solution were used as positive and negative controls, respectively. To avoid variations caused by the performance of the test, it was

TABLE I. Descriptive statistics of baseline symptom score and medication consumption in each group and comparative statistics (Mann-Whitney)

	Active	Placebo
Number of patients	41	19
Sex (M/F)	11/30	5/14
Age (y)		
Mean	34	33
Range	18-51	18-51
Skin test (μ g for 10 HEP)	0.56	0.65
Number of patients with asthma	13	6
Asthma severity	Mild	Mild

performed by the same trained allergist in the course of the trial. None of the patients was pretreated with drugs that could affect the results of the test. All of the reactions were recorded after 15 minutes of application.¹⁵ Wheal areas were outlined with a fine tip marker and transferred, with transparent tape, to the corresponding sheet of a case report form. The area of each wheal was measured by planimetry using a Wacom palette (Wacom Technology Co, Vancouver, Wash) and the computer program Mac Draft (Microspot, Inc, Boca Raton, Fla). For each patient, the dose of allergen extract needed to produce the same wheal size as the one induced by histamine HCl 10 mg/mL was calculated.²²

Rhinitis quality of life. The Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) developed by Juniper et al²³ was used in 2 occasions: the year previous to the trial, during the pollen season, and during the pollen season of the trial. Consistent with previous analyses, a change in score greater than 0.5 on the RQLQ domain and overall scores was the clinically meaningful minimal important difference.^{24,25}

Visual scale of health situation related to symptomatology. The visual scale of health situation related to symptomatology consisted of a 100-mm horizontal line with no intermediate marks or signs. The left end read, "VERY POOR," and the right end read, "VERY GOOD." The patients marked with a cross their clinical health situation related to symptomatology. This scale was filled before, during, and after the pollen season, at the end of the study.

Safety

The patients were instructed to report immediately any symptom appearing during the observation period. After injections, patients were supervised by physician in the hospital for at least 30 minutes. The patients were instructed to contact the physician if some side effects occur. The kind and intensity of all adverse events were documented in the case report form.

The reactions related to immunotherapy were categorized as immediate when the onset was during the first 30 minutes after the administration and delayed when the onset was after this time. Local reactions were quantified measuring the diameter of the reaction. The immediate reactions with a diameter of less than 5 cm and the delayed of less than 10 cm were considered clinically irrelevant, because a reduction in dose is not recommended.²⁶ The systemic reactions were graded following the European Academy of Allergology and Clinical Immunology Position Paper.²⁷

Statistical analyses

Determination of sample size. Assuming that the difference of symptom scores between both groups will be at least of 40%, and with an active to placebo ratio of 2:1, for $\alpha = 0.05$ (2-tailed) and $\beta = 0.2$ (1-tailed), the sample size must be 56 patients, divided into 2 groups:

37 patients in treatment (active) and 19 in the placebo group. Assuming a potential withdrawal rate of 15% to 20%, the sample size was adjusted to 66 patients, divided into 2 groups (44 on active and 22 on placebo).

The software SPSS (SPSS, Inc, Chicago, Ill) and Excel spreadsheet (Microsoft Corp, Seattle, Wash) were used for statistical analysis. The area under the curve (AUC) of each patient obtained during the pollen season was calculated for the symptom and medication scores. The median and the first and third quartile values (interquartile range) were used for descriptive statistics of symptom, medication scores, visual scale, and the 10 HEP values. The value of the mean and 95% CI was used for pollen counts and for quality of life (overall and each individual domains). Log-log regression in the bioassay of dose-response of *in vivo* SPTs was conducted²⁸ to calculate the 10 HEP values. Daily symptom and medication scores (AUC) during the pollination period,²⁹ RQLQ (overall and each domain), and the differences from the baseline in the individual 10 HEP were compared groupwise by using the nonparametric Mann-Whitney test. The Fisher exact *P* value was used to evaluate the differences between groups in the total number of days free of symptoms and rescue medication. The Hodges-Lehmann estimator (with the 95% lower and upper confidence limits) was used to measure the effect size of the differences between both groups of the values of the AUC of symptoms and medication scores.

RESULTS

Patient population

The demographic characteristics of the patients included in the study are shown in Table I. There were no significant differences regarding age, sex, skin test results, and prevalence of asthma in both groups.

Pollen counts

Chenopodiaceae and Amaranthaceae pollen counts were grouped together because of the difficulties in identifying individual members of these families. The level of 10 grains/m³ was considered as the limit for inducing symptoms in sensitized individuals.¹³ The detection of Chenopodiaceae and Amaranthaceae pollens started in mid-July and peaked from mid-August to mid-September. The median pollen count from August 15 to September 16 was 15.0 (IQ range, 9-15).

Symptom and medication scores

Patients were free of symptoms before and after the pollen season. None of the patients in the study needed to use oral steroids (prednisolone). This type of rescue medication was contemplated only for severe exacerbations. The use of as needed drugs was very low in both groups during the pollen season. The analysis of the data included the overall results of the study (from August 15 to September 16; Fig 1) and the data collected from September 1 to September 16. This period was selected because of a sharp increase in symptoms in the placebo group. The complete data set, including nasal, ocular, and chest and medication scores, is shown in Table II.

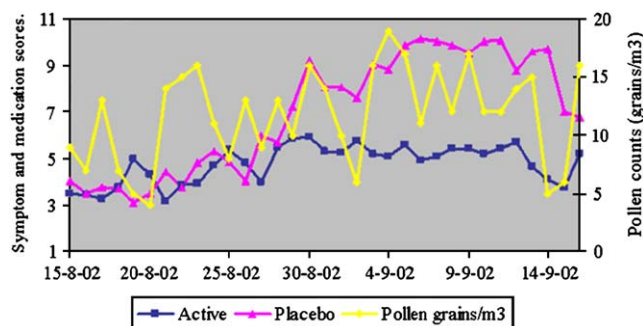


FIG 1. Total symptom plus medication scores of each group and pollen counts.

TABLE II. Descriptive statistics (median and IQ range) of the AUC of symptom score and medication consumption in each group and comparative statistics (Mann-Whitney and Hodges-Lehmann) during the pollen season

	Immunotherapy	Placebo	P value*	HL†
Median (first and third quartiles)				
From 8/15 to 9/16				
Total symptom score	4.3 (3.4-4.6)	6.4 (4.0-8.4)	<.001	-2.25 (-3.5, -0.8)
Nasal symptom score	3.0 (2.6-3.3)	4.5 (2.9-5.3)	<.001	-1.46 (-2.0, -0.6)
Ocular symptom score	1.0 (0.8-1.1)	0.8 (0.5-1.1)	.101	0.15 (-0.1, 0.3)
Bronchial symptom score	0.1 (0.1-0.2)	1.3 (0.6-1.5)	<.001	-1.07 (-1.3, -0.5)
Medication score	0.8 (0.7-0.8)	0.9 (0.5-1.1)	.115	-3.78 (-4.3, -2.7)‡
From 9/1 to 9/16				
Total symptom score	4.4 (4.3-4.6)	8.4 (7.5-8.8)	<.001	-3.96 (-4.3, -3.3)
Nasal symptom score	3.2 (3.0-3.5)	5.3 (5.0-5.5)	<.001	-2.08 (-2.4, -1.8)
Ocular symptom score	1.1 (1.0-1.1)	1.1 (0.9-1.5)	.669	-0.05 (-0.4, 0.1)
Bronchial symptom score	0.2 (0.2-0.3)	1.5 (1.4-1.6)	<.001	-1.28 (-1.4, -1.2)
Medication score	0.8 (0.7-0.8)	1.1 (1.0-1.2)	<.001	-0.32 (-0.4, -0.2)

*Mann-Whitney test.

†Hodges-Lehmann.

‡Although difference is not significant by the Mann-Whitney test, the Hodges-Lehmann test demonstrates that the difference is clinically relevant because the 0 value is not included in the 95% confidence limits.

Number of days free of symptoms and rescue medication

Period from August 15 to September 16. The 41 patients represented a total of 1230 days during this period, 368 of them without any symptom (29.9%). The 19 patients in placebo represented 570 days, 50 of them without any symptoms (8.7%; $P < .01$).

Period from September 1 to September 16. The 41 patients represented a total of 615 days during this period, 179 of them without any symptoms (29.1%). The 19 patients in placebo represented 285 days, 4 of them without any symptoms (1.4%; $P < .01$).

RQLQ

The results of the quality of life questionnaire are shown in Table III. There were no significant differences between both groups in the season previous to treatment, confirming the homogeneity of both groups. One year after, there was a significant difference ($P < .05$) between both groups in overall quality of life improvement and in the domains of activities, nasal symptoms, and emotions. Values greater than the minimal important difference (0.5) were

obtained for the overall quality of life and in all other domains, except for eye symptoms.

Visual scale

A box plot view of the visual scale results is shown in Fig 2. Before the pollen season, the median values were 9.00 (IQ range, 8.20-9.30) for the active group and 8.75 (IQ range, 6.80-9.58) for placebo ($P > .05$). During the pollen season, the median values were 7.00 (IQ range, 6.50-7.70) for the active group and 4.30 (IQ range, 3.43-4.90) for placebo ($P < .001$). After the pollen season, the median values were 9.35 (IQ range, 8.50-10.00) for the active group and 8.20 (IQ range, 7.10-9.25) for placebo ($P > .05$).

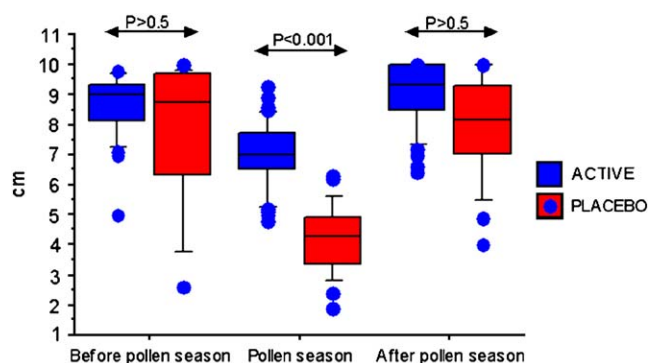
Skin test results

At baseline, the active group needed a median value of 0.56 mg (IQ range, 0.33-1.22) versus 0.65 (IQ range, 0.33-1.73; $P = .4$) in the placebo group for the 10 HEP value. At the end of the study, the median values were 1.49 mg (IQ range, 0.84-2.58) in the active versus 0.86 (IQ range, 0.49-1.88) in the placebo group ($P = .03$).

TABLE III. Descriptive statistics (mean and 95% CI) of the RQLQ (overall and domains), comparative statistics (Mann-Whitney), and difference of means

	Mean (95% confidence intervals)			
Quality of life	Active	Placebo	P value*	Difference of means
Pollen season before immunotherapy				
Activities	3.8 (3.2-4.3)	3.9 (3.2-4.5)	.631	−0.1
Sleep	2.2 (1.7-2.7)	2.4 (1.8-2.9)	.579	−0.2
Non−hay fever symptoms	2.0 (1.6-2.3)	2.0 (1.6-2.4)	.662	0
Practical problems	4.1 (3.7-4.4)	4.2 (3.6-4.9)	.554	−0.1
Nasal symptoms	3.5 (3.1-3.9)	3.8 (3.2-4.3)	.345	−0.3
Eye symptoms	2.6 (2.1-3.1)	2.4 (1.9-3.0)	.820	0.2
Emotions	1.7 (1.3-2.0)	1.8 (1.5-2.1)	.407	−0.1
Overall quality of life	2.8 (2.5-3.1)	2.8 (2.4-3.2)	.749	0
Pollen season of the study				
Activities	2.6 (3.0-2.1)	3.9 (4.4-3.4)	.002	1.30
Sleep	1.4 (1.7-1.1)	2.1 (2.8-1.4)	.321	0.80
Non−hay fever symptoms	1.7 (2.1-1.4)	2.3 (2.8-1.8)	.080	0.60
Practical problems	2.7 (3.2-2.3)	3.7 (4.4-3.0)	.073	1.00
Nasal symptoms	1.9 (2.2-1.5)	3.1 (3.8-2.3)	.008	1.20
Eye symptoms	1.6 (2.0-1.3)	1.9 (2.4-1.3)	.732	0.20
Emotions	1.2 (1.5-0.9)	1.8 (2.3-1.3)	.041	0.70
Overall quality of life	1.9 (2.2-1.6)	2.7 (3.2-2.2)	.017	0.80

*Mann-Whitney test.

**FIG 2.** Box plot view of the visual scale. The Y axis represents the median values of the visual scale.

Safety

All local reactions were delayed. There were 10 in 4 patients in the placebo group and 16 in 8 patients in the active group. From all of these, 8 reactions in the placebo group and 9 in the active group were subcutaneous nodules caused by aluminium hydroxide. The rest of the local reactions were clinically irrelevant (diameter < 10 cm). Four systemic delayed reactions occurred in 3 patients in the placebo group and 16 (4 immediate and 12 delayed) in the active group. All reactions were mild, of grade 2 (rhinoconjunctivitis or otic pruritus), and resolved without the need of medication.

DISCUSSION

This is the first double-blind, placebo-controlled study of efficacy (symptom and medication scores, quality of

life, skin reactivity, and visual scale analysis) and safety in a group of patients sensitized to *S kali*. Previously, only 3 reports had addressed the treatment of *S kali*-induced respiratory symptoms with immunotherapy.^{13,14,30} It is noteworthy that *S kali* is only one of the several species of the Chenopodiaceae/Amaranthaceae pollen families present in Zaragoza, which are all grouped together in aerobiological pollen surveys. Although a significant degree of cross-reactivity has been described between several members of these families, it is possible that other species, such as *Chenopodium* spp and *Amaranthus* spp, may be involved in the allergic response of these patients.³¹ A similar issue has been previously addressed for grasses. However, immunotherapy with a Timothy grass (*P pratense*), pollen extract proved to be more effective than a 4-grass mix.³² In this study, we have confirmed that treating patients who are sensitized to Chenopodiaceae with a modified *S kali* extract is efficacious in reducing

symptoms and improving quality of life parameters in this patient population.

This type of modified allergen extract has previously shown efficacy using *D pteronyssinus*,^{19,33} a mixture of *D pteronyssinus* and *D farinae*,³⁴ *O europaea*,³⁵ a mixture of *O europaea* and *Dactylis glomerata*,²⁶ and *P judaica*.³⁶ The safety of this vaccine has also been the subject of several comparative, controlled studies, demonstrating an excellent safety profile.³⁷⁻³⁹ In this study, the treatment was well tolerated, and no serious adverse effects were recorded. The local reactions were all delayed, small, and clinically not relevant. The majority of these reactions were subcutaneous nodules, which occurred at the site of injection. These nodules are a result of the aluminium hydroxide.⁴⁰ They may persist but usually disappear without the need of modify the immunotherapy dose and do not indicate that immunotherapy should be stopped. The treatment was not interrupted or the dose reduced during the *S kali* pollen season.

The primary endpoint in this study was the nasal, ocular, and bronchial symptom scores. After 1 year of treatment, there was a significant improvement in total symptom scores in the treated group. However, when individually analyzed, this difference was significant for nasal and bronchial symptoms and not significant for ocular symptoms. The Hodges-Lehmann estimator confirmed this finding, because the 0 value was not included in the 95% confidence limits for nasal, bronchial, and total symptom scores. The lack of significant improvement in ocular symptoms was also corroborated in the quality of life questionnaire, which suggests a good correlation between symptom scores and quality of life issues. Although this study was not powered to study efficacy on asthma, there were 19 patients with asthma in the study: 6 in the placebo and 13 in the active group. With the limitations mentioned, we detected significant differences in asthma symptoms between groups.

The standardized RQLQ developed by Juniper et al²³ was chosen as a secondary parameter and was used during the pollen season. It is now recognized that specific immunotherapy must also enable the patients to feel better and function better in their day-to-day lives.⁴¹ Quality of life is an outcome related to a fundamental aim of health care.⁴² This study suggests that immunotherapy improves quality of life of the patients, as has been previously suggested.^{18,29,33}

In the current study, we also observed a significant reduction in skin sensitivity in the active group when compared with placebo, confirming the overall improvement of the patients.

Immunotherapy with a depigmented and glutaraldehyde-polymerized extract of *S kali* pollen is safe and effective in the treatment of patients clinically sensitive to this pollen, as demonstrated by the significant reduction in symptoms (rhinoconjunctivitis and asthma), increase of days free of symptoms, reduction in drug consumption, improvement in rhinoconjunctivitis quality of life, reduction in skin sensitivity, and the values of the visual scale.

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