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Original article

Sublingual-swallow immunotherapy (SLIT) with a standardized five-grass-pollen extract (drops and sublingual tablets) versus placebo in seasonal rhinitis

Key words: asthma; five-grass-pollen extract; rhinoconjunctivitis; sublingual immunotherapy.

Background: Recent studies have demonstrated the efficacy of sublingual-swallow immunotherapy (SLIT) in seasonal and perennial rhinitis. Sublingual administration of solutions is not convenient for all patients. The aim of the study was to evaluate the efficacy and safety of immunotherapy administered sublingually, initially as drops, and then as tablets during maintenance therapy.

Methods: A total of 126 patients with grass-pollen seasonal rhinitis were included in this double-blind, randomized, placebo-controlled trial. During the progression of doses phase, the five-grass extract was given as sublingual drops from 1 to 100 IR/ml. Once the 100 IR dose was reached, the drops were replaced by a single 100-IR sublingual tablet per day.

Results: Throughout the grass-pollen season, patients in the active treatment group had significantly lower ($P<0.05$) total conjunctivitis and ocular redness scores. Rhinitis symptoms were not significantly different between the two groups. Patients given the active treatment were significantly ($P<0.02$) less likely to have asthma symptoms. The global medication score showed no significant difference between the two groups. A highly significant difference in favor of the active treatment group was seen in inhaled salbutamol use ($P<0.01$).

Conclusions: Clinical benefits achieved during the present study included significant improvements in conjunctivitis symptoms and prevention of asthma symptoms. The overall safety profile of the active treatment (drops or tablets) was good.

The medical literature on specific immunotherapy shows an increasing interest generated over the last 15 years by alternatives to subcutaneous injections, including the oral,

Table 1. Immunotherapy protocol

	Drops containing 1 IR/ml	Drops containing 10 IR/ml	Drops containing 100 IR/ml
Incremental dosing	1	1	1
phase	3	3	2
	6	6	4
	10	10	8
			12
			16
			20
Maintenance therapy	One 100-IR tablet/day		

sublingual, nasal, and bronchial routes, the goal being to improve safety and patient compliance. Sublingual immunotherapy has been the focus of many clinical studies (1). Early studies (2, 3) are difficult to interpret because they used low doses of allergens or nonstandardized allergen extracts. More recent, controlled studies of high-dose allergens have conclusively demonstrated that sublingual immunotherapy is effective in seasonal rhinoconjunctivitis (4–6, 8, 10, 11) and asthma (4, 6, 11), as well as in perennial rhinitis caused by house-dust mite (7, 9) and asthma (9). Proof of efficacy has not been obtained, however, in allergy to cat dander (12).

Sublingual administration of allergen extract solutions is not very easy for patients. A substantial improvement in patient compliance could be obtained by use of a sublingual tablet. From a pharmaceutical standpoint, the standardized allergen extract used to prepare the tablet is released in unchanged form during dissolution of the tablet.

This multicenter, double-blind, placebo-controlled trial evaluated the efficacy and safety of a five-grass-pollen allergen extract administered sublingually first as drops and then as tablets before and during the grass-pollen season to patients with seasonal rhinoconjunctivitis and in some cases with mild asthma. The primary efficacy criteria were the symptom and medication scores during the grass-pollen season.

Material and methods

Study design

This clinical study was conducted in accordance with good clinical practice guidelines and was approved by the Île-de-France-Paris Saint Antoine Ethics Committee. Written informed consent to participation in the study was obtained

from all adult patients and from the legal representatives of pediatric patients.

A multicenter, double-blind, randomized, placebo-controlled, parallel-group design was used. There were 20 study sites (five in the Paris area, nine in Nantes, two in Orléans, three in Valence, and one in Le Creusot). Screening procedures prior to study inclusion were conducted in January and February 1996. Patients who met all inclusion criteria were randomly assigned to active treatment or placebo. There was no run-in phase. The study treatment was given from March 1996 to July 1996. Patients attended three study visits, one at completion of the progression of doses phase (visit 2), one 6 weeks into the maintenance phase (visit 3), and one at treatment completion (visit 4). Patients could use medications for symptom control during the grass-pollen season. Mild symptoms were to be treated with flunisolide (Cassenne, Puteaux, France) as a nasal solution and by levocabastine (Chauvin SA, Montpellier, France) as ocular drops, moderate symptoms by 10 mg of cetirizine (UCB Pharma SA, Nanterre, France), and severe symptoms by oral prednisolone (Hoechst Houdé Paris-La Défense, France). Use of astemizole and mequitazine and/or cromones was prohibited during the trial. Patients with asthma were allowed to use inhaled salbutamol (Glaxo Wellcome, Paris, France).

Throughout the treatment, the patients were to record the following data every day in a diary: symptom intensity, symptomatic medication use, and study treatment administration. Before treatment initiation and at study completion, quantitative prick tests were done, and a blood sample was collected for antibody assays. At treatment completion, the physician and patient rated overall treatment efficacy on a four-point scale (successful, partial improvement, no change, and worse).

Patients

A total of 126 patients (109 adults, 17 children aged 7–15 years) with grass-pollen seasonal rhinitis were included in the study. There were 66 males and 60 females, with a mean age of 29 ± 11 years (range, 7–58 years). Of these 126 patients, 95 also had allergic conjunctivitis and 43 mild asthma. The diagnosis of grass-pollen allergy was based on a suggestive clinical history, a positive prick test to one of the pollens in the five-grass-pollen extract (Stallergènes SA, Antony, France), and a positive assay for specific IgE to orchard grass or timothy grass with the CAP System (Pharmacia Diagnostics, Uppsala, Sweden).

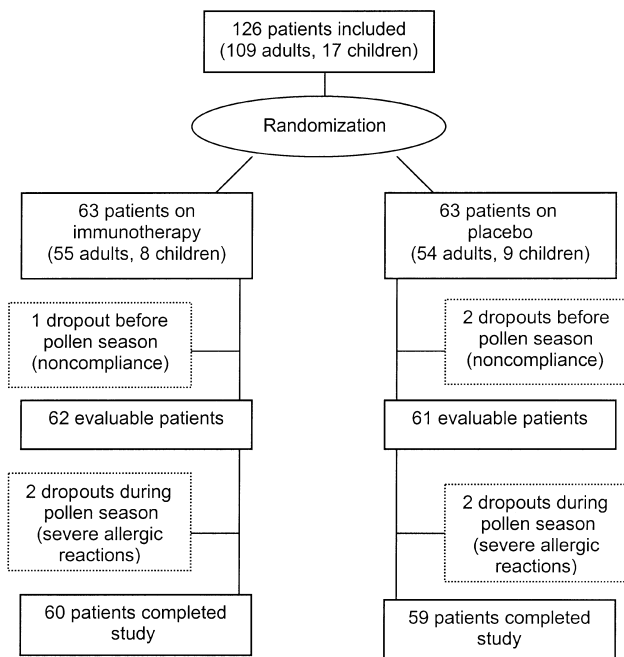


Figure 1. Study outline.

Exclusion criteria included clinically relevant sensitization to house-dust mites (*Dermatophagoides pteronyssinus*/*D. farinae*), cockroach, *Alternaria*, and pollens released during the same season as grass pollens. Allergy to cat and/or dog dander was an exclusion criterion only if the pet lived in the patient's home. Asthmatic patients whose treatment included medications other than β_2 -agonists taken as needed were excluded, as were patients who had received immunotherapy with one of the pollens in the five-grass-pollen extract within the last 2 years.

Allergen preparations

The standardized five-grass-pollen extract (Stallergènes SA, Antony, France) used throughout the study was a mixture of orchard grass, meadow grass, ryegrass, sweet vernal grass,

and timothy grass pollens. Its biologic activity was evaluated with RAST inhibition (13) in comparison with an internal standard in *in vitro* and *in vivo* tests, and was expressed as the index of reactivity (IR) defined as follows: a prick test with an extract containing 100 IR/ml produces a wheal with a mean geometric diameter of 7 mm in 30 patients sensitized to the allergen under consideration. The amount of the timothy major allergen Phl p 5 in 100-IR extract was 8.5 μ g/ml (dosage courtesy of Dr O. Cromwell, Allergopharma, Reinberg, Germany). This amount was greater than that measured in the batch used in a previous study (6.4 μ g/ml), but the variation was within the accepted range for in-house standardization (5).

Treatment

The treatment included a 15-day progression of doses phase (Table 1), during which the extract was given each morning as sublingual drops prepared with a glycerosaline diluent (Stallergènes SA, Antony, France) containing 1, then 10, and finally 100 IR/ml. The patients were instructed to keep the drops under the tongue for 2 min before swallowing them. When the 100-IR dose was reached (20 drops from the 100-IR/ml bottle), the drops were replaced by once-daily administration of a single sublingual tablet containing 100 IR, until 7 July 1996. The cumulative allergen dose in the active treatment group was about 11 000 IR corresponding to 0.935 mg of the timothy pollen major allergen Phl p 5. The placebo drops and tablets were similar to the active agent in terms of appearance, taste, and packaging. In both groups, the extract as sublingual drops was a limpid, colorless solution, with a sweet taste and smell. Active and placebo tablets were white, with a slightly sweet taste but no smell.

Symptom scores

Throughout the treatment period, rhinitis and conjunctivitis symptoms were recorded daily by the patients. Each symptom was rated on the following four-point scale: 0: no symptom; 1: mild; 2: moderate; up to 3: severe. Asthma symptoms were also recorded.

Patient diary data were used to calculate a daily total rhinitis symptom score (total, 0–12) based on four symptoms (rhinorrhea, nasal itching, nasal obstruction, and sneezing) and a daily total conjunctivitis symptom score (total, 0–9) based on three symptoms (tearing, ocular itching, and ocular redness). A mean daily score for each symptom and for the total rhinitis and conjunctivitis scores was calculated for each week of the grass-pollen season (29 April–7 July 1996).

Table 2. Demographic features in evaluable patients

	Active treatment	Placebo	
No. of patients	62	61	
Males/females	29/33	36/25	NS
Age (years)			
Mean $\pm$ SD	27.8 $\pm$ 10.6	29.7 $\pm$ 11.8	NS
Range	8–50	7–58	
Rhinitis duration, mean $\pm$ SD	9.4 $\pm$ 6.6	14.7 $\pm$ 8.6	$P < 0.001$
Personal history of asthma, n (%)	17 (27%)	25 (42%)	NS
Previous immunotherapy, n (%)	18 (29%)	19 (31%)	NS

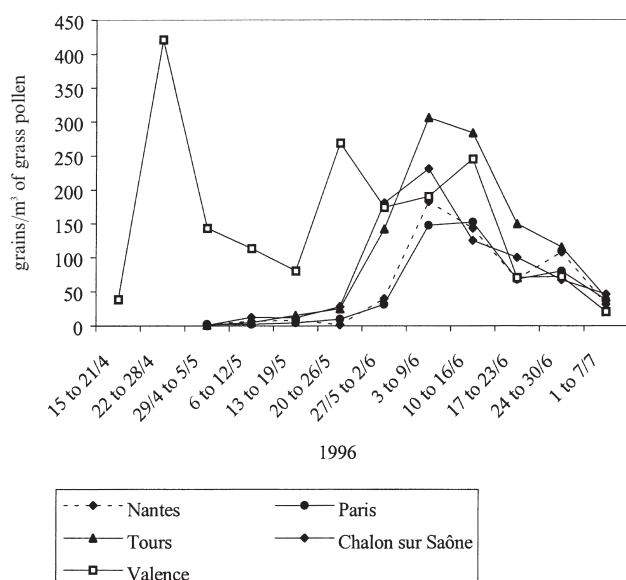


Figure 2. Grass-pollen counts for 1996 season.

Medication scores

Throughout the study, the patients were instructed to use symptomatic medications if needed and to record the amounts used. As described previously (5, 14), these diary data were used to calculate a global medication score that reflected total medication use by ascribing one point to each local application of antiallergic medication or puff of β_2 -agonist, two points to each tablet of antihistamine, and three points to each dose of oral prednisolone equivalent to 0.50 mg betamethasone. The number of patients who used each class of drugs at least once was also determined.

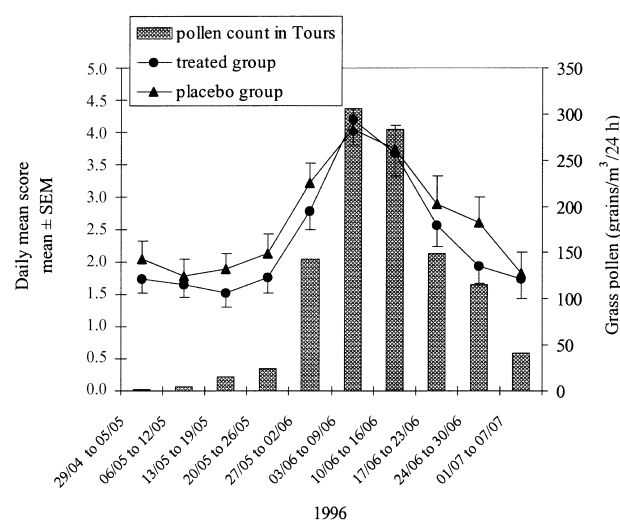


Figure 3. Total rhinitis symptom score (mean $\pm$ SEM) in relation to pollen counts.

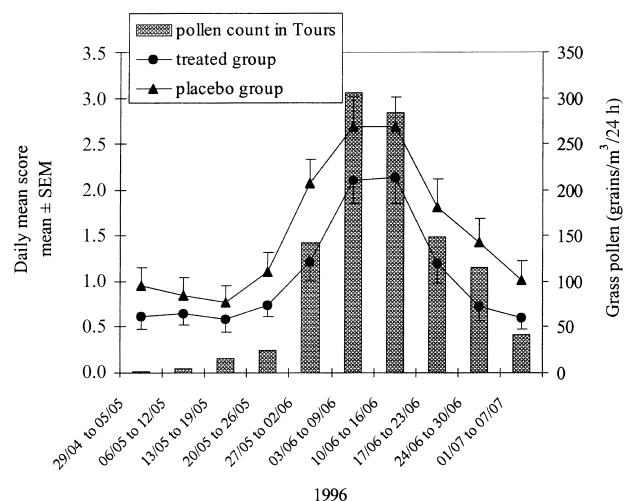


Figure 4. Total conjunctivitis symptom score (mean $\pm$ SEM, $P < 0.05$) in relation to pollen counts.

Prick tests

Quantitative prick tests were done at inclusion and at treatment completion with a five-grass-pollen allergen extract in concentrations of 6, 19, 56, 167, and 500 IR/ml. The five solutions were used according to a blind protocol. Prick tests were also done with a positive control (9% codeine phosphate) and a negative control (phenolated glycerosaline diluent). The Stallerpoint[®] device (Staller-gènes SA, Antony, France) was used to perform the prick test. Skin reactions were circled with a felt-tipped marker and then transferred by means of transparent tape to the case report form (CRF). Wheal diameters were measured along two perpendicular axes.

For each patient, the least-squares method was used to calculate the following regression line equation: $\text{Log}(y) = a + b \times \text{Log}(x)$, where y is the diameter of the wheal produced by each of the five concentrations and x the concentration in IR/ml of each of the five solutions. This regression line, which was the dose-response curve (concentration by wheal diameter), was used to calculate the theoretic wheal diameter obtained in response to a concentration of 100 IR/ml in each patient before and after treatment.

Laboratory tests

Timothy-specific IgE and IgG4 titers in sera collected before and after treatment were determined by the CAP System (Pharmacia Diagnostics, Uppsala, Sweden) and the RIA CAP System (Pharmacia Diagnostics, Uppsala, Sweden), respectively.

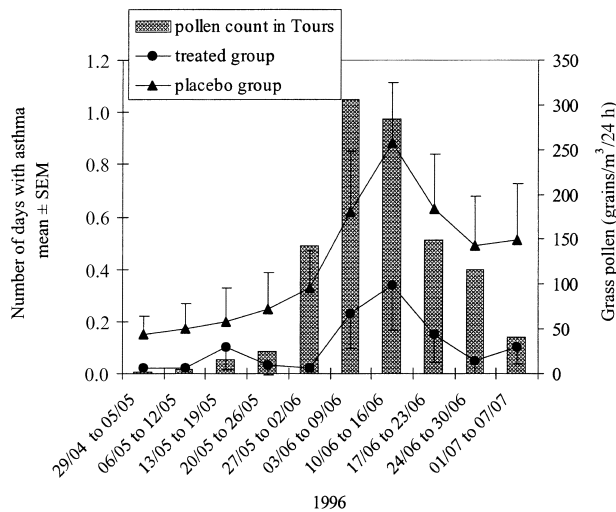


Figure 5. Number of days with asthma (mean $\pm$ SEM, $P < 0.02$) in relation to pollen counts.

Pollen counts

Pollen counts from the Pollen and Microenvironment Laboratory in Valence were used for the patients studied at the Valence study site. For the other four sites, pollen

counts were obtained from the National Aerobiological Surveillance Network of the Pasteur Institute in Paris.

Adverse events

The physician evaluated treatment safety at visits 2, 3, and 4 by asking the patient whether respiratory, cutaneous, or gastrointestinal symptoms had occurred since the last visit. All adverse events were to be recorded in the CRF irrespective of whether they were felt to be treatment-related.

Statistical methods

The chi-square test or Fisher's test was used for between-group comparisons of qualitative variables. Normally distributed quantitative variables were compared with Student's *t*-test. Non-normally distributed quantitative variables were compared with the Mann-Whitney U-test. Wilcoxon's T test was used for within-group comparisons of specific antibody levels. All tests were two-tailed, and the level of significance was set at 0.05.

Table 3. Between-group comparisons of symptom and medication use over entire pollen season

	<i>n</i>	Active treatment 62	Placebo 61	
Rhinitis symptoms				
Sneezing	mean ($\pm$ SD)	0.68 $\pm$ 0.47	0.77 $\pm$ 0.49	NS
Rhinorrhea	mean ($\pm$ SD)	0.72 $\pm$ 0.47	0.82 $\pm$ 0.57	NS
Nasal itching	mean ($\pm$ SD)	0.45 $\pm$ 0.50	0.52 $\pm$ 0.62	NS
Nasal obstruction	mean ($\pm$ SD)	0.49 $\pm$ 0.45	0.55 $\pm$ 0.62	NS
Total rhinitis score	mean ($\pm$ SD)	2.33 $\pm$ 1.61	2.65 $\pm$ 1.97	NS
Conjunctivitis symptoms				
Ocular redness	mean ($\pm$ SD)	0.33 $\pm$ 0.41	0.50 $\pm$ 0.53	$P < 0.05$
Ocular itching	mean ($\pm$ SD)	0.47 $\pm$ 0.44	0.62 $\pm$ 0.55	$P = 0.08$
Tearing	mean ($\pm$ SD)	0.27 $\pm$ 0.32	0.43 $\pm$ 0.54	$P = 0.05$
Total conjunctivitis symptom score	mean ($\pm$ SD)	1.06 $\pm$ 1.02	1.55 $\pm$ 1.53	$P < 0.05$
Asthma				
Number of patients who had asthma symptoms	<i>n</i> (%)	9 (15)	23 (38)	$P < 0.005$
Number of days with asthma symptoms	mean ($\pm$ SD)	1.1 $\pm$ 3.57	4.2 $\pm$ 9.28	$P < 0.02$
Medications				
Global medication score	mean ($\pm$ SD)	1.77 $\pm$ 2.27	2.13 $\pm$ 2.74	NS
Number of patients who used oral prednisolone	<i>n</i> (%)	12 (19)	21 (34)	$P = 0.059$
Number of patients who used inhaled salbutamol	<i>n</i> (%)	6 (10)	18 (30)	$P < 0.01$

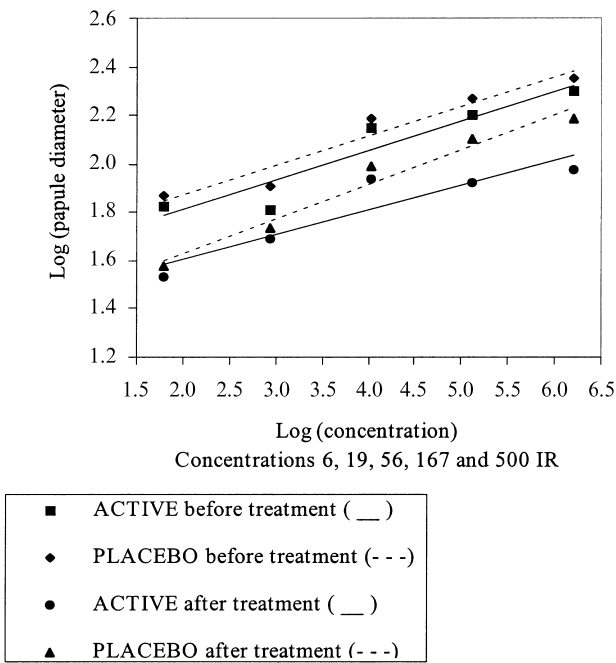


Figure 6. Quantitative prick tests: dose-response curves; i. e., mean wheal diameter in relation to allergen concentration (regression line after logarithmic transformation on abscissa and ordinate).

Results

Patients

The 126 included patients were randomly assigned to treatment with the active treatment (n=63: 55 adults and eight children; range: 8–15 years) or a placebo (n=63: 54 adults and nine children; range: 7–13 years). A scheme of the trial profile is shown in Fig. 1, according to CONSORT rules

(15). Three patients were excluded from the efficacy analysis because they were withdrawn for noncompliance from the trial before the pollen season. The demographic characteristics of the 123 evaluable patients (62 in the active treatment group and 61 in the placebo group) are shown in Table 2. No significant differences were found between the two groups in age, sex, asthma incidence, or sensitization to other allergens; however, rhinitis duration was significantly longer in the placebo group than in the active medication group ($P<0.001$, U test). Four patients (two in each group) were withdrawn from the study during the pollen season for reasons related to the allergic disorder (worsening symptoms, marked reactions). All the other patients completed the study.

Symptom scores

Pollen counts in Valence showed an early peak, from 22 to 28 April 1996. At all other collection sites, the pollen-count time curves were similar (Fig. 2) with a peak between 3 and 9 June 1996, followed by high counts from 10 to 16 June 1996. By taking the time curve of Tours as a reference, we found the symptom peaks to coincide with the pollen peaks in both groups (Figs. 3–5); this established the causative role of grass pollen in the symptoms. Marked differences in the conjunctivitis and asthma symptom curves in favor of the active treatment were seen. Both groups reported mild rhinitis symptoms before the beginning of the grass-pollen season because of sensitization to tree pollen released before grass pollen.

Table 4. Types and frequencies of adverse events

	Number of patients with adverse events	
	Active treatment	Placebo
Respiratory symptoms (total)	7	6
Tonsillitis/pharyngitis	1	1
Rhinitis	4	–
Bronchitis	–	1
Bronchospasm/dyspnea/asthma	2	4
Cutaneous symptoms (total)	6	2
Dermographism	–	1
Itching	4	1
Urticaria	2	–
Gastrointestinal symptoms (total)	2	2
Edema, burning sensation, or itching in oral cavity	9	1
Other	1	3

Symptoms persisted at a low level (Table 3) throughout the pollen season: for the entire pollen season, mean total scores in the active treatment and placebo groups were 2.33 and 2.65 for rhinitis and 1.06 and 1.55 for conjunctivitis, respectively. For the pollen season overall, no significant between-group differences were found for rhinitis symptoms, although all mean scores were slightly lower in the active treatment group (Table 3). In contrast, symptoms of conjunctivitis were significantly reduced in the active treatment group vs the placebo group, with significant differences for the total conjunctivitis score ($P<0.05$, *t*-test) and the ocular redness score ($P<0.05$), as well as borderline differences for the tearing score ($P=0.05$) and ocular itching score ($P=0.08$). Furthermore, the number of days with asthma symptoms was significantly smaller in the active treatment group than in the placebo group: 1.1 vs 4.2 days, respectively, for the entire pollen season ($P<0.02$, *t*-test). The proportion of patients who experienced asthma symptoms at least once during the pollen season was significantly smaller ($P<0.005$, chi-square test) in the active treatment group (15%) than in the placebo group (38%) (Table 3). At inclusion, the proportion of patients with a history of asthma was higher in the placebo group than in the active treatment group (42% vs 27%), although the difference was not statistically significant. Adjusting for a personal history of asthma did not abolish the significant between-group differences in the number of days with asthma and the proportion of patients with asthma at least once during the pollen season ($P<0.05$). With some exceptions (four active, seven placebo), patients who experienced bronchial asthma during the study were the same who had presented asthma in previous seasons. Most probably, asthma was previously underdiagnosed.

Medication scores

The global medication score for the entire pollen season was lower in the active treatment group, although the difference was not statistically significant (Table 3). Use of oral antihistamines and local symptomatic treatments (flunisolide and levocabastine) was limited in both treatment groups, reflecting the low level of symptoms overall, with no significant between-group differences (data not shown).

Oral prednisolone, the first-line rescue medication for severe symptoms, was required in 19% of active treatment patients vs 34% of placebo patients (Table 3). This difference was almost significant ($P=0.059$, chi-square test) despite the small amount of prednisolone used (mean $\pm$ SD, 0.65 ± 1.75 and 1.41 ± 3.60 mg/day for the entire pollen

season in the active treatment and placebo groups, respectively). It should be pointed out that two of the 21 placebo-group patients who used prednisolone received an injectable corticosteroid in addition to oral prednisolone.

Inhaled salbutamol use on at least one occasion during the pollen season was required in 10% of the active treatment patients vs 30% of the placebo patients (Table 3). This highly significant difference ($P<0.01$, chi-square test) was directly correlated with the number of days with asthma, which was higher in the placebo group; the difference remained significant after adjustment for a personal history of asthma ($P<0.05$).

The overall efficacy ratings by the patient and physician at study completion usually indicated partial improvement, with no significant difference between the two groups.

Prick tests

Mean wheal diameter size in response to a concentration of 100 IR/ml predicted by the dose-response curve was not significantly different between the two groups at baseline or after treatment completion, nor was there any significant difference in variations from baseline to treatment completion. Nevertheless, a larger decrease in wheal diameter was seen in the active treatment group (-1.44 mm) than in the placebo group (-0.88 mm). The dose-response curves at baseline (Fig. 6) were almost parallel and very close to each other, indicating that skin reactivity was comparable in the two groups. The post-treatment regression lines were located under the baseline regression lines in both groups, attesting to a global decrease in skin reactivity. Furthermore, after treatment, the lines were no longer parallel: the slope of the line was less steep in the active treatment group, reflecting a decrease in skin reactivity to high concentrations that contrasted with the increase seen in the placebo group.

Laboratory tests

Timothy-specific IgE titers increased significantly in the active treatment group, from 91.3 ± 239.9 kIU/l at baseline to 244.5 ± 459.1 kIU/l after treatment ($P<0.0001$, Wilcoxon's T test). In the placebo group, timothy-specific IgE increased significantly from 78.8 ± 105.9 kIU/l at baseline to 144.0 ± 231.0 kIU/l after treatment ($P<0.0001$). The increase in timothy-specific IgE in the placebo group was significantly smaller than in the active treatment group ($P<0.04$, Mann-Whitney U-test). Similar results were found for timothy-specific IgG4 titers, which increased in the

active treatment group from $5.7 \pm 3.8\%$ at baseline to $8.7 \pm 10.9\%$ after treatment ($P < 0.0001$, Wilcoxon's T test). In the placebo group, timothy-specific IgG4 increased significantly from $6.0 \pm 3.3\%$ at baseline to $6.8 \pm 4.5\%$ after treatment ($P = 0.002$). The IgG4 increase was significantly smaller in the placebo group ($P < 0.03$) than in the active treatment group. There was no correlation between IgE, IgG4 levels, IgG4/IgE ratio, and symptoms and/or drug scores within both groups of patients.

Safety

Most patients tolerated the study treatment well. Numbers of patients with at least one adverse event were not significantly different between the two groups (27% in the active treatment group and 19% in the placebo group). In both groups, adverse events fell into four main categories: respiratory, cutaneous, gastrointestinal, and buccolingual (Table 4). Seventeen patients (15 adults and two children) in the active group reported adverse events. Usually, the events appeared a few minutes after administration of drops containing 100 IR/ml or tablets. Respiratory effects (sneezing, rhinitis, or dyspnea) were minor and of short duration (from a few minutes to 1 h) except for patient no. 107, who was withdrawn from the trial because his rhinitis symptoms increased after each treatment intake for at least 12 h. Cutaneous signs (hand, under-chin, or ear itching) were minor and lasted at most 1 h except for patient 32 (15 years old), who was withdrawn after generalized urticaria which lasted 48 h. Only one patient reported a gastrointestinal effect (diarrhea occurring during the progression phase and lasting for 2 weeks). Minor buccopharyngeal effects were the main side-effects documented (four occurrences of labial or buccal tickling after drops intake, and five occurrences of itching and edema in the oral cavity, mainly after tablets intake): they affected nine patients (eight adults and one child, 12 years old) and were brief (maximum 90 min). There was no demographic difference between the patients who presented adverse reactions and those who did not.

Discussion

This multicenter study compared a five-grass-pollen allergen extract administered sublingually as drops and then as tablets with placebo. Patients were selected according to strict inclusion criteria. They received allergen doses (cumulative dose of about 11 000 IR in $4\frac{1}{2}$ months of

treatment) about 150 times higher than those generally administered by the parenteral route.

The primary efficacy criteria were the symptom and medication scores during the pollen season. Patients were allowed to use rescue medications if needed. Use during the entire pollen season of antihistamines and local symptomatic treatments was not significantly different between the two groups. This indicates that the symptom score differences in favor of the active treatment group were not due to rescue medication use. Rescue medications kept rhinitis and conjunctivitis scores at a low level in both groups, leaving little room for a further decrease due to the study treatment. Nevertheless, the total conjunctivitis score was significantly lower ($P < 0.05$) in the active treatment group than in the placebo group, although this was not associated with a significant improvement in the rhinitis symptoms. Although the assessment of asthma symptoms was not the primary criterion in this study, the results showed significantly less symptomatic asthma in the active treatment group than in the placebo group ($P < 0.02$). Consistent with this difference was a highly significant decrease in inhaled salbutamol use in the active treatment group ($P < 0.01$).

Earlier clinical studies (4, 6, 9, 11) found that specific immunotherapy could have a prophylactic effect against bronchial symptoms in patients with allergic rhinitis or rhinoconjunctivitis. Casanovas et al. reported a significant decrease in dyspnea during the pollen-count peak in patients treated before the pollen season with *Olea europaea* extract given sublingually, as compared to placebo, but the difference was not significant for sneezing and nasal obstruction (4). Similarly, in a study by Vourdas et al., children treated with a sublingual olive-pollen extract for 2 years before and during the pollen season had a significantly lower dyspnea score during the two consecutive pollen seasons than children given placebo (11). However, the difference between the two groups was not significant for rhinitis in any of the treatment years; conjunctivitis symptoms were significantly lower in the active treatment group only at the pollinic peak during year 2. Feliziani et al. reported a significant reduction in both rhinoconjunctivitis and asthmatic symptoms in patients who received pre- and coseasonal treatment with grass-pollen extracts (6). In a study evaluating the efficacy of sublingual immunotherapy in children with asthma or rhinitis caused by house-dust mite, Tari et al. found a significant decrease in specific and nonspecific bronchial hyperreactivity after 12 months of treatment (9). In addition, in the present study, use of oral corticosteroid therapy over the entire pollen season showed a difference that approached statistical significance in favor

of the active treatment group. The amount of oral corticosteroids used was halved in the specific immunotherapy group. This finding corroborates results obtained by Clavel et al. (5) in 120 patients with grass-pollen allergy in a double-blind, placebo-controlled study of sublingual-swallow immunotherapy (SLIT) given before and during the pollen season up to a maintenance dose of 300 IR/day: the amount of oral corticosteroids used during the season and the number of patients who used corticosteroids at the time of the pollen-count peak were significantly decreased in the active treatment group. The global medication score was also significantly lower in the SLIT group than in the placebo group. However, Clavel et al. did not find any significant difference between groups for rhinitis and conjunctivitis symptoms.

The cumulative allergen dose in the present study was about 11 000 IR, which is more than 150 times the dose administered during subcutaneous immunotherapy of similar duration. Nevertheless, no increase in the adverse event rate was seen in the active treatment group. Most adverse events were mild oral cavity reactions that did not require treatment. The rate of side-effects in the active group (27% of patients) was similar to those seen during earlier studies: 24% in Vourdas et al.'s study (11), 29% in Clavel et al.'s study (5), and 34% in Sabbah et al.'s study (8). Two active treatment patients had to stop the treatment because of severe allergic reactions (worsening of urticaria and rhinitis), but two placebo patients were also removed from the study, for bronchospasm and dermatographism. In contrast to injection immunotherapy, no anaphylaxis reaction was reported, and the most frequent adverse event was due to the exposure of the sublingual mucosa to the allergen extract.

The decreases in conjunctivitis and asthma symptoms achieved during the present study corroborate findings from other studies using allergen doses 5–500 times higher than those used for subcutaneous immunotherapy (5, 8–10). Sabbah et al. (8) evaluated the efficacy of sublingual immunotherapy with a five-grass-pollen extract in a dose 50 times that used subcutaneously in 58 patients with seasonal rhinoconjunctivitis; significant differences in favor of the treatment vs the placebo were found for rhinoconjunctivitis symptoms and rescue medication use. However, these studies did not define accurately the amount of allergen needed.

In the present study, several factors may explain the absence of statistically significant differences in rhinitis scores between the two groups. First, it is possible that the preseasonal period of treatment and the total duration of treatment (4½ months) were too short, so that the

cumulative dosage received by the patient was not sufficient. The placebo effect seen in the present study and in many immunotherapy studies (2) may have masked the differences in terms of efficacy. In Clavel et al.'s study (5), the cumulative dosage was 40 700 IR, corresponding to 2.6 mg of the timothy pollen major allergen Phl p 5, as opposed to 11 000 IR, corresponding to 0.935 mg of the major allergen in the present study. However, despite a lower dose of allergens than that used by Clavel et al., better clinical results were obtained with regard to conjunctivitis symptoms, which were significantly lower in the active group. This difference could be related to the use of sublingual tablets, a factor that might considerably improve patient compliance. Second, grass-pollen counts during 1996 were much lower than those reported in other studies performed in different years in the same country (5, 8) or in another one (6); thus, rhinitis and conjunctivitis symptoms stayed at a low level in both groups, even during the pollinic peak. Third, the large multicenter design of this study, involving 20 study sites and five different areas, may have masked the treatment effect and interfered with the interpretation of results. Fourth, the groups were not homogeneous in duration of rhinitis and history of asthma at the inclusion. There should have been a baseline period with monitoring of symptoms and drug scores for a season before randomization to ensure an equal balance of disease severity in the active and placebo groups. For all these reasons, our results are not inconsistent with prior studies demonstrating the clinical efficacy of sublingual immunotherapy in patients with allergic rhinitis.

The significant specific IgE and IgG4 titer increase seen in the present study and in earlier works (5, 9, 10) provides further evidence that sublingual immunotherapy has an effect on the immune system. Because of the influence of two factors, the effect of specific immunotherapy and the exposure to grass pollen, the increase in specific IgE and IgG4 was greater in the SLIT group than in the placebo group.

The mechanism of action of sublingual immunotherapy is not completely elucidated, however. According to one of the current hypotheses, tolerance may be induced via Langerhans' cells that internalize the antigen in the sublingual mucosa before migrating to the regional lymph nodes, where they act as antigen-presenting cells. This may result in T-cell response changes responsible for oral tolerance (16). The mechanisms of action of specific immunotherapy have been far more extensively studied for the subcutaneous than the sublingual route: several studies have established that venom immunotherapy was associated with decreased IL-4 production and increased IFN- γ production (17, 18).

The efficacy of immunotherapy may be related to a Th2-to-Th1 switch, although the mechanism underlying this switch remains controversial.

In conclusion, this clinical study demonstrated that this route of administration is safe and provides clinical benefits including significant improvements in conjunctivitis symptoms and prevention of asthma symptoms.

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