

Double-blind, placebo-controlled evaluation of sublingual immunotherapy with standardized olive pollen extract in pediatric patients with allergic rhinoconjunctivitis and mild asthma due to olive pollen sensitization

Vourdas D, Syrigou E, Potamianou P, Carat F, Batard T, André C, Papageorgiou PS. Double-blind, placebo-controlled evaluation of sublingual immunotherapy with standardized olive pollen extract in pediatric patients with allergic rhinoconjunctivitis and mild asthma due to olive pollen sensitization.

Allergy 1998; 53: 662–672. © Munksgaard 1998.

**D. Vourdas¹, E. Syrigou¹,
P. Potamianou¹, F. Carat²,
T. Batard², C. André²,
P. S. Papageorgiou¹**

¹P. & A. Kyriakou Hospital, Athens, Greece;

²Stallergènes, Antony, France

For evaluation of the efficacy and the safety of specific sublingual immunotherapy with high allergen dose, 66 children with seasonal asthma, rhinitis, and conjunctivitis due to sensitization to olive pollen were enrolled in a double-blind, randomized, placebo-controlled study between October 1994 and October 1996 in Greece. Thirty-four patients were randomly allocated to the active group, and 32 received placebo. Immunotherapy consisted of olive-allergen extracts (Stallergènes SA) administered sublingually pre- and coseasonally from January to July for 2 consecutive years. Serial concentrations from 1 to 300 IR were used up to the maintenance dose of 20 drops of 300 IR daily. The cumulative dose for each patient was 300 times higher than in parenteral immunotherapy, and the cumulative dose of the major allergen Ole e 1 was 8.1 mg/2 years. The patients were assessed by clinical parameters (symptom and medication scores from patients' daily diaries) and immunologic measurements (specific IgE, IgG4, eosinophil cationic protein [ECP]) were performed. The actively treated patients had a significantly lower score for dyspnea ($P < 0.04$ during the first season; $P < 0.03$ during the second season). At the pollinic peak during the second year, a lower score of conjunctivitis was recorded ($P < 0.05$) in the actively treated patients. The analysis of intragroup evolution showed that the total score of rhinitis increased significantly during the pollinic peak in the group under placebo, whereas there was no symptomatic peak for the same period in the group under active treatment. However, the difference between the groups was not significant. The medication score did not differ significantly between the groups. Oral steroids were the only variables with a P value near the significance level ($P = 0.06$) in favor of the actively treated group. A significant decrease in skin reactivity was recorded in the active group after 2 years of treatment. No significant variation in specific IgE and IgG4 was detected. A significantly lower level of serum ECP was observed at the pollinic peak in the actively treated patients during the first pollen season ($P = 0.01$), but this was not confirmed the second year when the ECP levels doubled in both groups without correlation to the clinical findings. Tolerance was excellent with only a few minor side-effects reported. In conclusion, high-dose specific sublingual immunotherapy appears to be safe and effective in improving mild seasonal asthma and conjunctivitis linked to olive-pollen sensitization.

Key words: asthma; children; olive allergy; rhinoconjunctivitis; sublingual immunotherapy.

Photini Saxonis Papageorgiou, MD
Allergy Unit
P. & A. Kyriakou Children's Hospital
GR-115 27 Athens
Greece

Accepted for publication 12 February 1998

Immunotherapy has been used extensively since 1911 (1) as a specific treatment of allergy. Double-blind studies have shown the efficacy of injection with pollen or mite extracts as a treatment of allergic rhinitis and conjunctivitis as well as allergic asthma (2). In the last decade, the clinical practice of immunotherapy has changed significantly. With the overall aim of improving the safety of immunotherapy and making it more convenient to patients, routes other than subcutaneous administration of allergens have been investigated.

One of them is the sublingual route. Several placebo-controlled studies have shown the efficacy and safety of such a treatment, but further studies are required to establish the place of sublingual immunotherapy in the treatment of allergic diseases.

Olive pollen is one of the most important allergen sources in countries with a Mediterranean climate (3). Since the olive is a cultivated tree, the prevalence of olive pollinosis may vary considerably from region to region within the same climatic environment, depending on the quantity of cultivation of this tree.

The sensitizing capacity and clinical relevance of *Olea europaea* allergens, mainly Ole e 1, has been studied by a number of investigators. The olive tree has a short, usually well-defined pollination period, lasting about 1 month. The frequency of skin positivity to *O. europaea* pollen allergens in subjects from the Mediterranean area with suspected atopic respiratory allergy has been reported as 15% in southern France (4), 13–30% in Italy (5, 6), 36% in Spain (7), and 37% in Greece (8). Olive pollinosis in adults and children is clinically characterized by rhinoconjunctivitis and/or bronchial asthma (9). These symptoms mostly occur in association and less frequently as isolated manifestations (6).

Immunotherapy has been widely employed in the treatment of olive allergy; nevertheless, its effects have been poorly investigated from both a clinical and a laboratory point of view.

As for sublingual immunotherapy with this allergen, only one double-blind, placebo-controlled study, by a Spanish team (10), has been reported. The most important finding in that study was that during the pollinic season the group treated with placebo developed significantly more dyspnea than the group treated with extract ($P=0.0285$). In terms of rhinoconjunctivitis symptoms, skin prick test measurements before and after immunotherapy, and *in vitro* tests, no significant difference was recorded. The small number of patients (six in the placebo group and nine in the active group) and the too short preseasonal period of immunotherapy administration were the shortcomings of this study.

Therefore, we designed a double-blind, placebo-controlled trial with high doses of olive-pollen extract in aqueous solution, to be administered by the sublingual route in children suffering from rhinitis and/or asthma due to allergy to olive pollen. The short pollination period of *O. europaea* seemed to offer an advantage, as this was likely to increase the compliance of the study patients.

The objective of the study was to compare the efficacy of sublingual immunotherapy with a standardized olive-pollen extract with that of placebo in children with allergic rhinoconjunctivitis and/or mild asthma due to olive-pollen sensitization.

Material and methods

Study design

The study was conducted according to Good Clinical Practice (GCP) rules, with the informed consent of the patients' parents and the authorization of the ethics committee of the P. & A. Kyriakou Children's Hospital and the Greek health authorities. The study was designed in a double-blind, placebo-controlled, parallel-group fashion. Fig. 1 illustrates the study design. Preselection of the patients was done during the olive pollen season in spring 1994. Patients enrolled in the trial between October 1994 and January 1995 were allocated to receive either the active or placebo sublingual therapy.

The study ran for 2 consecutive years (October 1994–October 1996), the sublingual therapy being administered pre- and coseasonally from January to July each year.

Regular visits were scheduled for clinical evaluation and safety assessment. Quantitative skin prick tests were performed before the treatment start, after 1 year, and at the end of the trial.

Blood samples for immunologic measurements were taken before the treatment started, after 1 year of the trial, at the end of the study, and in the middle of each pollinic season (in May of each year of the study).

Patients

Sixty-nine patients with a positive history of rhinoconjunctivitis and/or mild asthma due to sensitization to olive pollen proved by positive skin prick tests and positive RAST class II and above were preselected in April–May 1994 and enrolled in the trial in October 1994 until January 1995.

Patients who had uncontrolled asthma or symptomatic polysensitization, or who were taking beta-blockers or retard corticosteroids were excluded. Three patients were withdrawn before the begin-

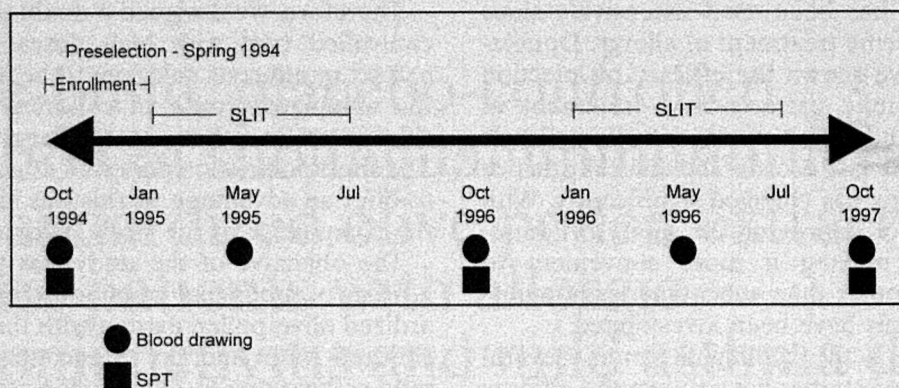


Fig. 1. Study design. SLIT: sublingual immunotherapy; SPT: skin prick test.

Table 1. Clinical characteristics of patients

	Active treatment (n=34)	Placebo (n=32)
Sex		
M	25	24
F	9	8
Age (years)		
Mean	12	12
Range	8–17	7–17
Clinical features		
Asthma plus rhinitis	33	29
Rhinitis without asthma	1	3
Associated conjunctivitis	32	27
Duration of allergic disease		
Mean	4	4
Range	2–8	2–8

ning of treatment (two for inadequate cooperation and one for intercurrent illness).

The 66 patients continuing the study were randomly assigned to the active treatment (34 patients) or placebo (32 patients). Table 1 shows the characteristics of the two groups of patients. There was no difference between groups in demographic variables. The treatment groups were homogeneous in case history (rhinoconjunctivitis and mild asthma symptoms), respiratory function, and immunologic parameters.

Treatment

The active treatment was a standardized olive pollen extract (Stallergènes SA). The biologic unit used by Stallergènes SA to label its extracts is the index of reactivity (IR). In-house reference extract (labeled 100 IR) is defined as the concentration eliciting a wheal of 7 mm mean diameter in 30 skin-prick-tested allergic patients.

The major allergen Ole e 1 was 13.5 µg/ml (100 IR/ml). Four concentrations of the allergen were used: 1, 10, 100, and 300 IR/ml.

The placebo was a glycerinated phenolated saline solution with an appearance similar to that of the active agent.

Patients received drops to be taken each morning sublingually and held under the tongue for 2 min before being swallowed.

The treatment was started in January 1995 with two drops of the lowest concentration (1 IR/ml), increasing by two drops per day up to a maximum of 10 drops/day. The treatment continued with two drops of the next concentration (10 IR/ml), increasing by two drops per day up to 10 drops/day, and then progressing in a similar way from two to 20 drops of the next concentration (100 IR/ml) and then of the highest concentration (300 IR/ml). The maintenance dose was 20 drops of 300 IR/ml daily for 5 months. In July, the treatment was stopped until the next January. The same schedule was used for the second season of the trial.

The cumulative dose of allergenic extract received by each patient was 30 000 IR per year (300 times higher than in parenteral specific immunotherapy). The cumulative dose of major allergen Ole e 1 was 4.05 mg/year.

Patient monitoring

Symptom-medication score. Patients were instructed to keep a diary during the pollen season for the daily evaluation of symptoms on a 0–3 grading scale (0=no symptoms, 1=mild, 2=moderate, up to 3=severe symptoms), covering nasal symptoms (sneezing, rhinorrhea, or blockage), eye symptoms (itching, redness, or weeping), and lung symptoms (cough, dyspnea, or wheezing). The patients were allowed to use antiallergic and antiasthmatic drugs, when necessary, as summarized in Table 2. The patients had to record in the diary card any use of drugs for symptom treatment, and a specific score was given in relation to the class of drugs (1 point for local antiallergic treatment, 2 points for each

Table 2. Drugs allowed during pollen season

Drug	Dosage
Cetirizine	10 mg/24 h
Salbutamol	200 µg q.i.d.
Terbutaline	500 µg q.i.d.
Theophylline	16 mg/kg/day
Disodium cromoglycate	
Eye-drops 2%	1 drop t.i.d.-q.i.d.
Nasal spray 2%	2 puffs t.i.d.-q.i.d.
Aerosol forte 5 mg	2 puffs t.i.d.-q.i.d.
Capsules 20 mg	1 capsule t.i.d.-q.i.d.
Budesonide	
Nasal spray 50 µg/puff	2 puffs b.i.d.
Turbuhaler 200 µg/puff	2 puffs b.i.d.
Prednisolone	1–2 mg/kg/24 h

antihistamine administration and each puff of inhaled corticosteroids, and 3 points for each oral corticosteroid tablet). All the patients were given a mini-Wright Peak-Flow Meter (Clement Clarke International, UK) and instructed to perform PEF determination and registration twice a day during the pollen season.

At each visit, the patients and the physician made an overall evaluation of the treatment on a scale of results noted as 1 (much better), 2 (better), 3 (unchanged), and 4 (worse).

Skin prick tests

At the inclusion visit, skin prick tests with other allergens (grasses, *Parietaria*, *Dermatophagoides pteronyssinus*, *Alternaria*, and cockroach) were performed to evaluate cosensitization to olive pollen. A positive control (solution of 9% codeine phosphate) and a negative control were used.

Quantitative skin prick tests with five dilutions (100, 60, 20, 6.6, and 0.2 IR) of olive-pollen extract were performed in duplicates on the patients' forearms before the treatment started, and 1 year and 2 years after the treatment began.

All the skin reactions were recorded 20 min after administration of prick tests. The wheals were outlined with a fine-tip rollerball pen and transferred by means of transparent tape to the corresponding sheet of the Case Report Form (CRF). The geometric means of the diameters of wheals induced by each concentration, measured with a scanner, were used to draw for each patient the dose-response curve by the method of least squares: $\log A = a + b \times \log C$ (where A =diameter of the wheal, a =intercept, b =slope, C =concentration). Any wheal having a diameter of 0 was given a value of 1 mm.

In vitro parameters

Allergen-specific IgE, allergen-specific IgG4, and serum eosinophil cationic protein (ECP) were

Table 3. Distribution of polysensitized patients and types of allergens

	Active group	Placebo group
No. of patients	34	32
Polysensitized patients	30	26
Allergens		
Grass	23	15
<i>Parietaria</i>	11	10
<i>Alternaria</i>	12	9
Mite	5	9

measured by means of commercial kits according to the supplier's instructions (Pharmacia AB, Uppsala, Sweden) in samples of sera taken before the start of treatment, after 1 year of the trial, at the end of the study, and in the middle of each pollen season (in May of each year of the study).

Safety assessment

According to GCP rules, investigators were asked to record in detail any adverse effects, whether or not related to the treatment. The side-effects were classified according to the Position Paper of the Immunotherapy Subcommittee of the European Academy of Allergology and Clinical Immunology (EAACI).

Pollen count

The pollination season of the olive in Greece starts at the beginning of May and lasts until the end of June. The evolution of pollen grain counts was recorded in Athens for each year of the study during the pollen season with a Burkard Sampler (Burkard Manufacturing Co.).

Statistical analysis

Nonparametric analysis of data involved the use of the Wilcoxon test for intragroup comparison and the Mann-Whitney test for intergroup comparison. The statistical tests comparing two entities were two-tailed; $P < 0.05$ was considered significant.

Results

Patients

Out of 66 randomized patients, one patient from the active group was withdrawn from the trial during the first pollen season due to worsening of allergic disease and one patient from the placebo group at the patient's wish. Therefore, only 64 patients (33 of the active group and 31 of the placebo group) were analyzed for efficacy, but all 66 patients were included in the tolerance analysis.

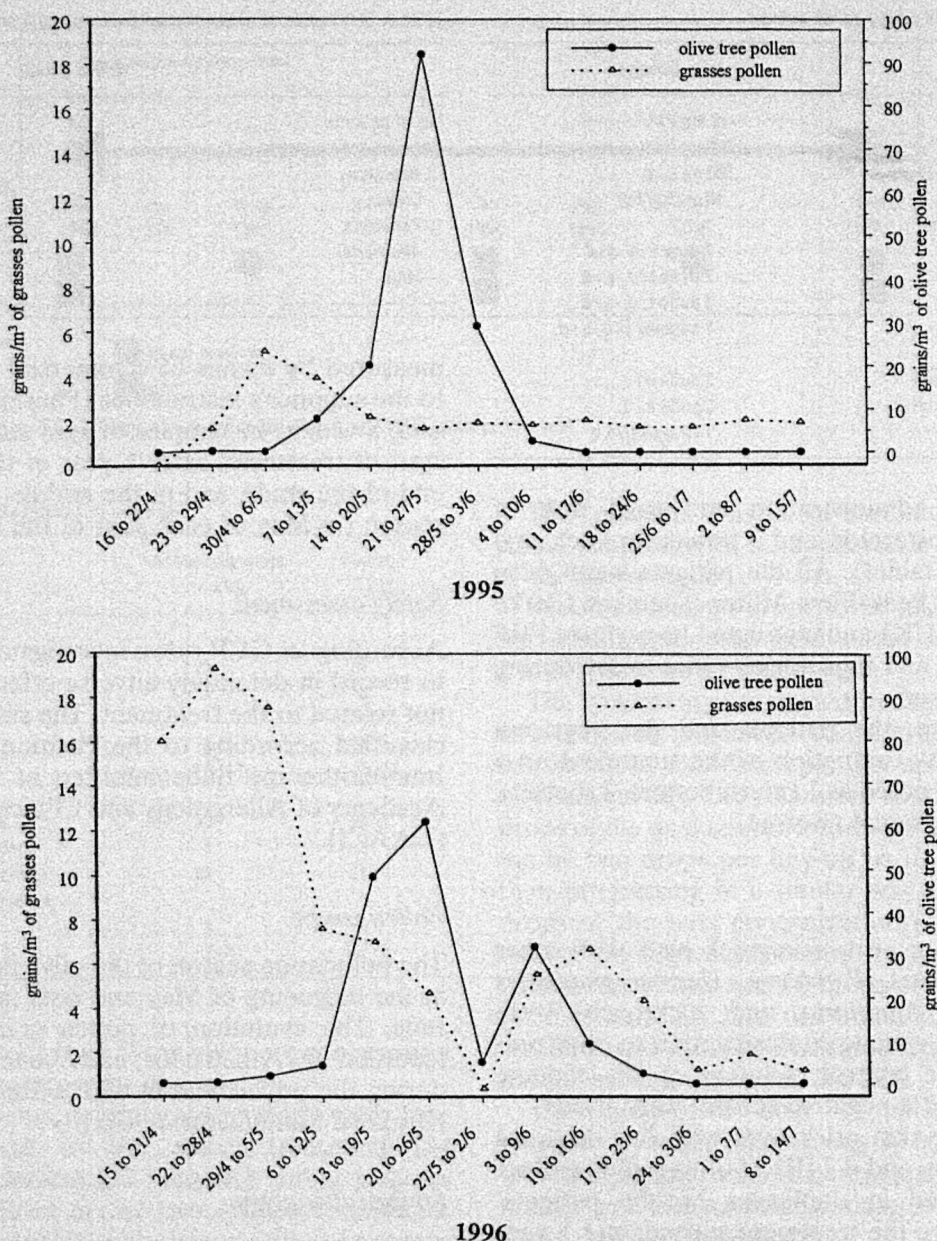


Fig. 2. Pollen counts (olive and grass).

At the inclusion visit, 62 patients (33 in the active group and 29 in the placebo group) had been suffering from mild asthma for at least 2 years, and four patients (one in the active group and three in the placebo group) were suffering only from rhinoconjunctivitis. During the second season, two nonasthmatic patients, both from the placebo group, experienced asthma symptoms. Therefore, 62 patients were asthmatic, and only two patients, one in the active group and one in the placebo group, had no asthma symptoms during the study. Half of the patients (23 in the active group and 15 in the placebo group) were cosensitized to grass pollens, and very few to other allergens. Table 3 shows the number and distribution of polysensi-

tized patients and the type of allergen. However, in Greece, the olive pollen season is different from that of grass pollen, peaking in middle May, unlike the grass pollen season, which usually peaks in April. Our patients were asymptomatic in April, and their symptoms peaked consistently in mid-May during the preceding 2–4 years. This established the causative role of olive pollen in their symptoms.

Pollen counts

Pollen count data for olive pollen showed some differences between the 2 years of the study. The first had higher absolute counts but for a relatively

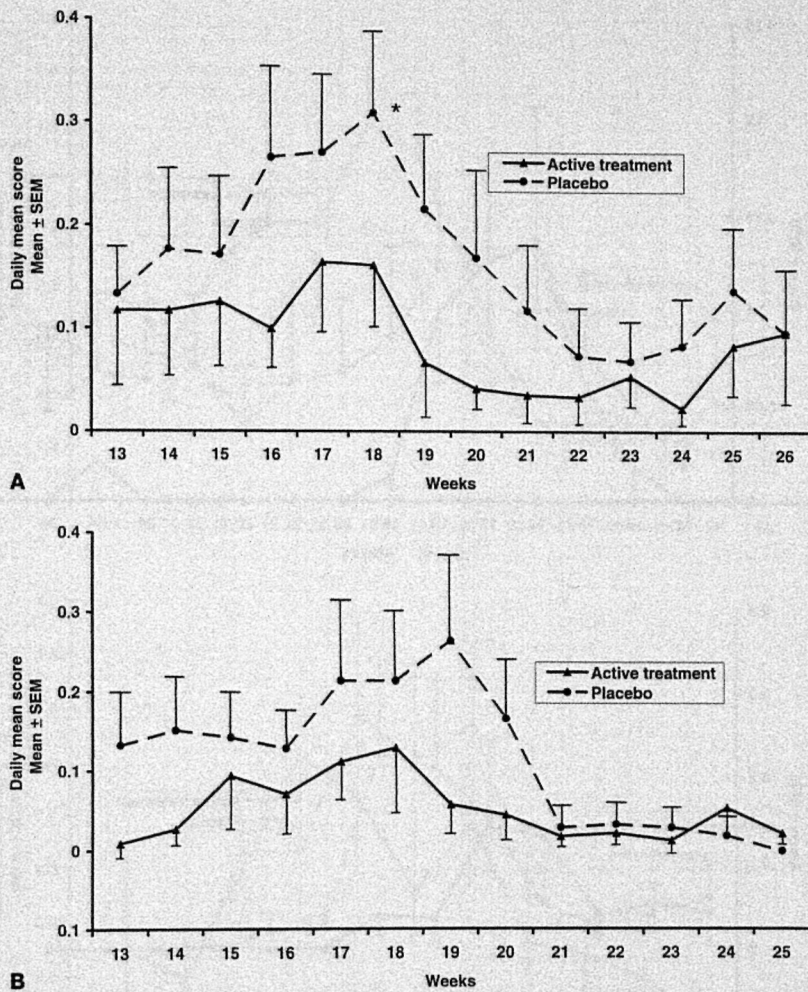


Fig. 3A. Dyspnea during first olive pollen season (1995) ($P < 0.04$).

Fig. 3B. Dyspnea during second olive pollen season (1996) ($P < 0.03$).

short period. The second season had lower absolute counts but for a longer period of time (Fig. 2). Fig. 2 also depicts a concomitant grass-pollen curve showing marked variability between the 2 years.

Clinical parameters of efficacy assessment

Primary variables to assess efficacy were symptomatology of allergic disease and symptomatic drug intake recorded on diary cards by patients. The actively treated patients had a significantly ($P < 0.04$) lower score of dyspnea (49% less than placebo) during the first pollinic peak (Fig. 3A), and this tendency continued ($P < 0.03$) during the second season (Fig. 3B). A significantly ($P < 0.05$) lower score for conjunctivitis (85% less than placebo) was recorded in the actively treated patients only at the pollinic peak during the second year (Fig. 4A and B).

The analysis of intragroup evolution showed that the total score of rhinitis increased significantly during the pollinic peak in the group under placebo,

whereas there was no symptomatic peak for the same period in the group under active treatment. However, the difference between the groups was not significant in any of the treatment years (Fig. 5A and B). No difference in peak expiratory flow rate (PEFR) between groups was noted. The average PEFR level was better after the pollination season than before in both groups. The medication score did not differ significantly between the groups. Oral steroids were the only variables with a P value near the significance level ($P = 0.06$) in favor of the actively treated group.

Global evaluation by the patients themselves and the physician showed that patient condition frequently improved, but treatment groups did not differ significantly in these variables.

Skin prick tests

The groups were compared by means of the nonparametric Mann-Whitney test on the diameter of the

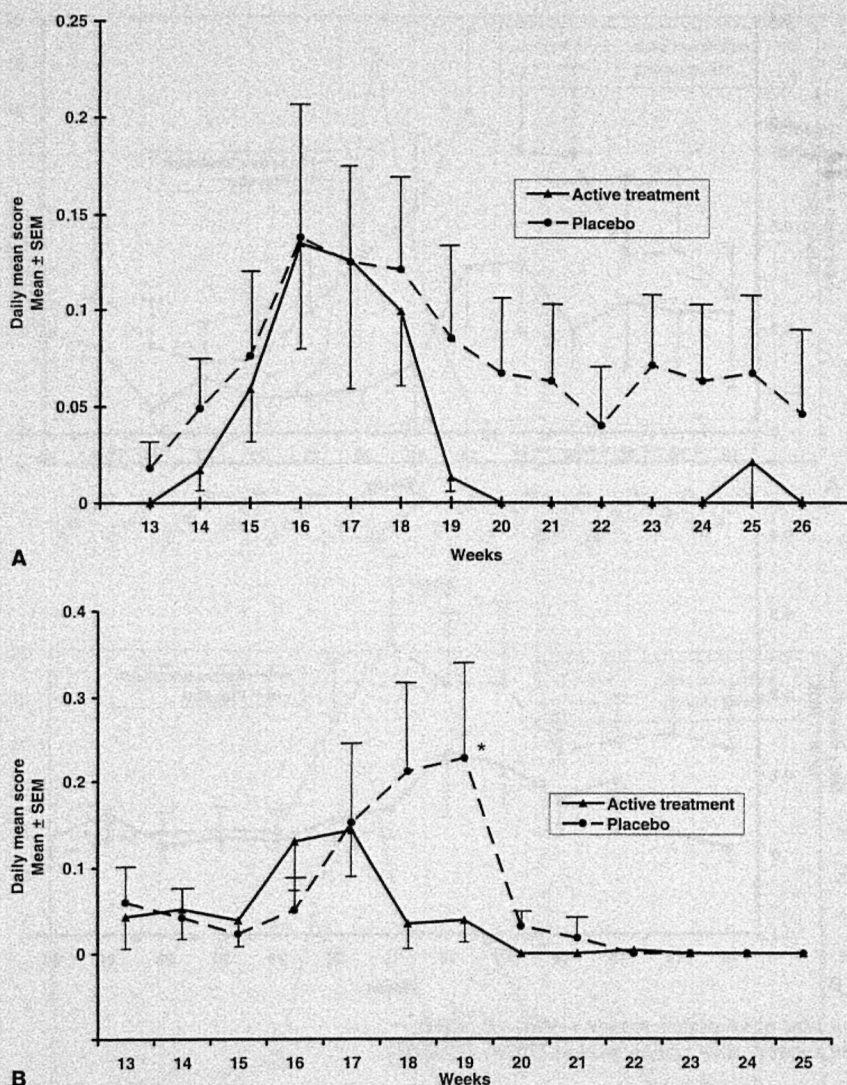


Fig. 4A. Eye redness during first olive pollen season (1995) ($P < 0.05$).

Fig. 4B. Eye redness during second olive pollen season (1996) ($P < 0.05$).

wheel obtained with the concentration of 100 IR on the dose-response curve estimated by regression analysis before the start of treatment, after 1 year, and after 2 years. A significant difference ($P < 0.03$) was observed only after 2 years, as shown in Table 4.

In vitro parameters

Specific IgE value. No significant variation of specific IgE concentration was detected.

Specific IgG4 value. The evolution of IgG4, similar in both groups, was unusual, as, after an initial increase during the first pollinic season, the values decreased in both groups.

ECP value. A significantly lower level of serum ECP was observed at the first pollinic peak in the

actively treated patient ($P = 0.012$), but this was not confirmed the second year, when the ECP levels doubled in both groups without correlation with the clinical findings (Table 5).

Side-effects

Immunotherapy was globally well tolerated. No major adverse event was reported. A few minor adverse events were reported only during the progression phase for eight patients in the active group (eight occurrences of buccal itching or oropharyngeal pruritus, one labial swelling, and conjunctivitis symptoms) and two patients in the placebo group (buccal itching, labial swelling). One tablet of cetirizine (10 mg) was administered in only one patient. In all but one patient with side-effects, the dosage was reduced temporarily, and

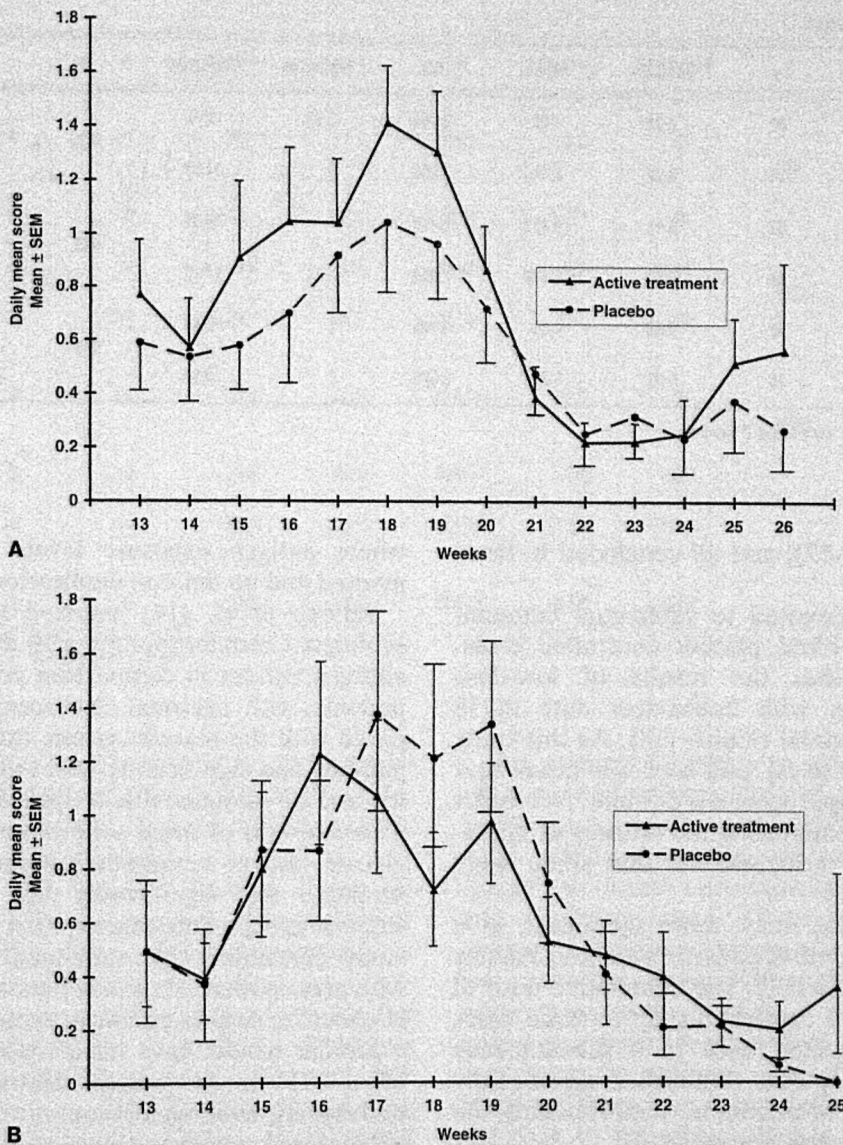


Fig. 5A. Rhinitis symptoms during first olive pollen season (1995).

Fig. 5B. Rhinitis symptoms during second olive pollen season (1996).

reached the final dose with a delay. In one patient, the optimum maintenance dose was lower than the one suggested by the manufacturer.

Discussion

In this study, the efficacy of sublingual immunotherapy with a standardized olive-pollen extract was assessed in comparison to placebo in children with allergic rhinoconjunctivitis and/or mild asthma due to sensitization to olive pollen. Sublingual immunotherapy can be delivered by a sublingual-spit method or in a sublingual-swallow fashion (11). However, only the sublingual-swallow method has demonstrated evidence of clinical efficacy.

The present study showed clinical improvement of asthma and conjunctivitis symptoms, thus supporting the clinical efficacy of sublingual immunotherapy with a high dose of allergen administered in a sublingual-swallow fashion. The total cumulative dose was 300 times higher than in classical subcutaneous immunotherapy, with excellent tolerance.

A number of other controlled studies have reported results of the treatment of allergic disorders by sublingual immunotherapy. It is difficult to compare these results because of the great variability in the duration of treatment, the amount of allergen-extract administration, the number and type of patients, and the allergen used. However, most of these results showed evidence of clinical

Table 4. Skin reactivity evolution

		<i>n</i>	Median	Mean	SD	Minimum	Maximum	U	<i>z_c</i>	<i>P</i>
Before treatment	Active	33	7.32	7.62	2.314	3.99	13.5	425	-1.162	NS
	Placebo	31	8.92	8.15	2.404	3	11.69			
One year after	Active	32	6.41	6.172	2.298	1	10.37	443	-0.9265	NS
	Placebo	32	6.92	6.788	1.954	2.71	11.03			
Two years after	Active	33	4.59	4.56	2.478	1	12.44	318	-2.0851	0.0371
	Placebo	28	5.62	5.71	2.528	1	9.94			

U: Mann-Whitney U test; *Z_c*: corrected Z for ties.

improvement (12–17), and all concluded in favor of safety.

The first trial devoted to sublingual immunotherapy, a double-blind, placebo-controlled, cross-over trial, describes the results of low-dose sublingual therapy with house-dust mite in 18 patients with perennial rhinitis (18). As this study was very brief (15 days), and used low doses near the homeopathic approach, it is difficult to consider it as significantly supporting the efficacy of immunotherapy. Many criticisms of this study were expressed (19, 20).

Another trial was much more significant, as it focused on a group of 40 patients with seasonal hay fever for 24 months (12). The cumulative dose of grass-maize pollen extract rose up to three times the classically injected dose in a subcutaneous protocol. The symptoms diminished significantly after the first year of treatment. Unfortunately, the drug consumption was not recorded.

Tari et al. assessed the efficacy of sublingual immunotherapy in 58 patients under 12 years of age suffering from asthma and rhinitis due to mites (13). The treatment lasted 18 months, and the quantity of aqueous extract of mites was five times higher than in classical subcutaneous immunotherapy. A significant reduction of the nasal and respiratory symptom score was already observed after 12 months of treatment, and it became even higher after 18 months of treatment. The same significant difference between groups was demonstrated in medicine consumption. In the active group, more than half of the patients had a reduction of 20% or more in medicine consumption.

The only double-blind, placebo-controlled study on sublingual-spit was carried out in cat-allergic patients (21). The results of this study cannot be analyzed because of methodological problems, as the challenge was performed in a room with cats

where antigen exposure levels were not documented and no data on medication score provided.

Sabbah et al. (14) assessed the efficiency of sublingual immunotherapy with drops of five-grass allergen extract in comparison with placebo in 58 patients with seasonal rhinoconjunctivitis. Compared with the placebo group, the actively treated patients had significantly fewer symptoms of rhinitis and of conjunctivitis during the pollen season. Consumption of nasal solution of sodium cromoglycate and of betamethasone and dexchlorpheniramine was significantly less in the actively treated group. Side-effects were negligible. This study concluded that sublingual immunotherapy with grass-pollen extracts in patients with hay fever is effective, easy to perform, economical, and safe.

Similar results have been reported by Feliziani et al. (15) in 34 patients allergic to grass and undergoing sublingual immunotherapy in a rush preseasonal schedule followed by a maintenance dose administered three times a week until the end of the pollen season. In a double-blind, placebo-controlled study using another allergen (*Parietaria* pollen) in 31 rhinitic patients, Troise et al. (16) showed that the actively treated patients had a significantly lower medication score than those on placebo at the pollinic peak. Furthermore, at the end of the trial, a significant decrease in nasal reactivity ($P < 0.02$) was also recorded.

A carefully designed (double-blind, double-dummy) study conducted by an Italian team (17), using grass-pollen extracts, compared the efficacy of sublingual immunotherapy with the traditional injection immunotherapy. The results showed that sublingual and injective therapy was equally effective, according to subjective clinical parameters, with a statistically highly significant ($P = 0.002$) reduction of symptoms and drugs. However, the complete lack of side-effects in the conventional injection immunotherapy group and the absence of

Table 5. ECP dosage

		<i>n</i>	Median	Mean	SD	Minimum	Maximum	U	<i>z_c</i>	<i>P</i>
First season										
ECP	A	34	10.5	17.1	21.09	3.2	85	532	-0.1541	0.88 (NS)
before season	B	32	10	12.4	8.69	2.7	44			
ECP during	A	34	18.5	25.5	25.46	6.5	150	323.5	-2.5109	0.0120
pollinic peak	B	30	27	33.1	21.19	12	100			
Second season										
ECP	A	32	14.18	24.42	24.518	2.71	95	455.5	-0.35	0.73 (NS)
before season	B	30	13.06	28.38	29.295	2.33	99.7			
ECP during	A	32	56.07	52.23	29.215	11.83	99.41	461	-0.27	0.79 (NS)
pollinic peak	B	30	49.99	53.47	34.055	10.16	150.6			

U: Mann-Whitney U test; *Z_c*: corrected Z for ties.

a placebo group in the Quirino et al. study might interfere with the interpretation of their results. The objective parameters changed only in patients treated with injective therapy.

According to the EAACI Position Paper on Immunotherapy (22), the optimal study design for investigating clinical efficacy includes pretreatment monitoring of symptom and drug score for a season. In this study, preselection of patients for the study was done during the immediately preceding season while the patients were symptomatic. But they did not use diary cards for accurate grading of their symptom score, a procedure which would have resulted in a definitive group identification. However, the duration of the study for 2 years and the distribution of patients in terms of age and disease symptoms (almost all asthmatic patients) increased the possibility of correctly balanced groups (Table 1). The number of polysensitized patients was also equally distributed among active and placebo groups. The most important cosensitization was grass pollen (Table 3). However, the peak olive pollen season is different from that of grass pollen (Fig. 2). Unlike the grass pollen season, which tends to be variable and long, the olive pollen season is very short in Greece, peaking every year around 20 May. As a result, patients with symptomatic sensitization to olive pollen have a very well-defined period of symptoms. Our patients during the preceding 2–4 years were asymptomatic in April with symptoms peaking in middle May. This establishes the causative role of olive pollen in our patients' symptoms.

The primary variables to assess efficacy in this study were symptomatology of allergic disease and symptomatic rescue drug intake. In contrast to most published studies on sublingual immunotherapy, we found a discrepancy between symptom and medicine score. There was no difference between control and active group in either season for medication score. Although there is no ready explanation of this finding, it is possible that patients were primed to aggressive treatment of symptoms from the previous years. It is of interest that some symptoms were recorded in the diaries before the peak of the olive pollen in both seasons. This might be due to the underrecording of olive pollen by our collection method. Rantio-Lehtimäki et al. (23) found daily counts of most pollen types higher on the ground than at roof level. *Artemisia* and grass pollen were detected 1–2 weeks earlier at ground level than on the roof. These authors conclude that especially the beginning of flowering should be monitored at a low level. For the present study, the Burkard sampler was located 20 m above the ground. In addition, recording of pollen counts in only one station of the Athens area might also affect the accuracy of the pollen curve, particularly at the beginning of the season.

The side-effects noted in this study were negligible, as has been found in most studies including mainly adult patients. The increased number of side-effects, some of them severe, reported by Tari et al. (13) in children with mite asthma and rhinitis may be due to the type of allergen used in children with perennial asthma. Side-effects have been

reported to be higher in asthmatic patients during conventional mite injection immunotherapy (24).

Comparison of the objective data, including skin reactivity, ECP, specific IgE, and IgG4, showed a significant difference only in skin reactivity. A decrease in skin reactivity was recorded after 2 years of treatment. This finding is in contrast to other published studies in sublingual immunotherapy. Perhaps, the long duration of our study and the large number of patients account for this difference. Quirino et al. (17) found a decrease of skin reactivity approaching statistical significance ($P=0.071$) only after 6–12 months of sublingual immunotherapy, with a sample size of only 10 patients. As in other studies, no significant variation or correlation between *in vitro* immunologic parameters has been found. No change in IgG4 was found during sublingual immunotherapy by Quirino et al., who showed that the objective parameters changed only in patients treated with injection immunotherapy. These discrepancies between the clinical and objective parameters observed in the present study and in several others could be interpreted as a consequence of the mechanism of action, which seems to be different for sublingual immunotherapy and the injectable one. More data on the mechanisms are necessary.

A larger investigation is definitely needed to draw final conclusions on the place of sublingual immunotherapy in the routine treatment of allergic disease. However, our study on sublingual immunotherapy in olive-allergic children with asthma provides evidence of the clinical benefit of this type of immunotherapy, which is cheaper and more attractive to the young patient than conventional immunotherapy, especially for short-term pollinosis.

References

- Noon L. Prophylactic inoculation against hay fever. *Lancet* 1911;1:1572-3.
- Greenberger PA. Use of immunotherapy for allergic disorders. *Immunol Allergy Clin North Am* 1992;12:1-12.
- D'Amato G, Lobefalo G. Allergenic pollens in the southern Mediterranean area. *J Allergy Clin Immunol* 1989;83:116-22.
- Bousquet J, Cour P, Guerin B, Michel FB. Allergy in the Mediterranean area. I. Pollen counts and pollinosis of Montpellier. *Clin Allergy* 1984;14:249-58.
- Fanti A, Giosue S, Bizarri F. Pollinosis a Romanel periodo 1984-1986. *Folia Allergol Immunol Clin* 1989;36:149-55.
- Liccardi G, Tusso M, Saggese M, et al. Clinical significance of allergic sensitization to *Olea europaea* I pollen in Naples area, Italy. *Aerobiologia* 1994;8:34-7.
- Guera F, Daza JC, Miguel R, Moreno C, Aviles C, Sanchez Guijo P. Evolution of pollinosis in our province: 10-year clinical results. *Allergy* 1992;47 Suppl:72.
- Gioulekas D, Chatzigeorgiou G, Likogiannis S, Papakosta D, Mpalaftoutis C, Spieksma FThM. *Olea europaea* 3-year pollen record in the area of Thessaloniki, Greece and its sensitizing significance. *Aerobiologia* 1991;7:57-61.
- D'Amato G, Liccardi G. Pollen related allergy in the European Mediterranean area. *Clin Exp Allergy* 1994;24:210-19.
- Casanova M, Guera F, Moreno C, Miguel R, Daza JC. Double-blind, placebo-controlled clinical trial of pre-seasonal treatment with allergenic extracts of *Olea europaea* pollen administered sublingually. *J Invest Allergol Clin Immunol* 1994;4:305-14.
- Malling H-J. Sublingual immunotherapy. *Clin Exp Allergy* 1996;26:1228-31.
- van Niekerk CH, De Wet JJ. Efficacy of grass-maize pollen oral immunotherapy in patients with seasonal hay-fever: a double-blind study. *Clin Allergy* 1987;17:507-13.
- Tari MG, Mancino M, Monti G. Efficacy of sublingual immunotherapy in patients with rhinitis and asthma due to house dust mite. A double-blind study. *Allergol Immunopathol (Madr)* 1990;18:277-84.
- Sabbah A, Hassoun S, Le Sellin J, André C, Sicard H. A double-blind placebo-controlled trial by the sublingual route of immunotherapy with a standardized grass pollen extract. *Allergy* 1994;49:309-13.
- Feliziani V, Lattuada G, Parmiani S, Dall'Aglio PP. Safety and efficacy of sublingual rush immunotherapy with grass allergen extracts. A double-blind study. *Allergol Immunopathol (Madr)* 1995;23:224-30.
- Troise C, Voltolini S, Canessa A, Pecora S, Negrini AC. Sublingual immunotherapy in *Parietaria* pollen induced rhinitis: a double-blind study. *J Invest Allergol Clin Immunol* 1995;5:25-30.
- Quirino T, Iemoli E, Siciliani E, Parmiani S, Milazzo F. Sublingual versus injective immunotherapy in grass pollen allergic patients. *Clin Exp Allergy* 1996;26:1253-61.
- Brostoff J, Scadding GK. Low dose sublingual therapy in patients with allergen rhinitis due to house dust mite. *Clin Allergy* 1986;16:483-91.
- Warner JO. Low dose sublingual therapy in patients with allergic rhinitis due to house dust mite. *Clin Allergy* 1986;16:387-8.
- Amlstedt S, Dreborg S, Einarsson R. Sublingual therapy for allergic rhinitis. *Clin Allergy* 1987;17:85-8.
- Nelson HS, Oppenheimer J, Vatsia GA. A double-blind, placebo-controlled evaluation of sublingual immunotherapy with standardized cat extract. *J Allergy Clin Immunol* 1993;92:229-36.
- Malling H-J, Weeke B. Position paper. Immunotherapy. *Allergy* 1993;48 Suppl 14:9-35.
- Rantio-Lehtimäki A, Koivikko A, Kupias R, Mäkinen Y, Pohjola A. Significance of sampling height of airborne particles for aerobiological information. *Allergy* 1991;46:68-76.
- Lockey RF, Benedict LM, Turkeltaub PC, Bukantz SC. Fatalities from immunotherapy (IT) and skin testing (ST). *J Allergy Clin Immunol* 1987;79:660-77.

This document is a scanned copy of a printed document. No warranty is given about the accuracy of the copy. Users should refer to the original published version of the material.