

A double-blind, placebo-controlled trial by the sublingual route of immunotherapy with a standardized grass pollen extract

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Fifty-eight patients with well-documented history of seasonal rhinoconjunctivitis caused by grass pollens were allocated randomly on a double-blind basis to receive either sublingual therapy with a solution of purified, standardized allergen preparation (Stallergènes) or a matched placebo for 17 weeks. The assessment of the effect of oral immunotherapy, done with drops of five-grass allergen extract, was on the clinical symptoms and on the medication score of the authorized rescue treatments. The actively treated patients had significantly ($P < 0.05$ to $P < 0.01$) fewer symptoms of rhinitis (sneezing and rhinorrhea) and of conjunctivitis (redness and tears) during the pollen season than the placebo group. Consumption of nasal solution of sodium cromoglycate and of betamethasone and dexchlorpheniramine was significantly less in the desensitized group ($P < 0.01$). Side-effects were negligible. This study concludes that perlingual immunotherapy with grass pollen extract in grass-pollen-sensitive seasonal hay fever and conjunctivitis patients is effective, easy to perform, inexpensive, and safe.

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Many controlled studies have been devoted to assessment of the efficacy of specific immunotherapy by the subcutaneous route. Allergen immunotherapy is an efficient form of treatment for patients with allergic rhinitis, IgE-mediated asthma, and venom hypersensitivity (10). On the contrary, few controlled studies have evaluated the efficacy of immunotherapy where the desensitization treatment was administered by the oral or sublingual route.

Both positive (2, 3, 7, 16–18) and disappointing (5, 6, 15) results have been reported, but, generally, the procedure has been shown to be efficacious although not always absolutely safe (8). It has been observed that the efficacy of the treatment appears to be linked to the highest doses, and it seems to be likely that the sublingual route may be safer even if less efficacious than the subcutaneous route (12). This may meet the objections of the UK Committee of Safety of Medicines (4). On the other hand, the European Academy of Allergology and Clinical Immunology (EAACI) Immunotherapy Subcommittee has recently stated that more conclusive data are required before sublingual immunotherapy can be recommended for routine treatment of allergic disorders (14).

Therefore, the aim of the present study was to determine the efficiency of desensitization by pollen extracts administered sublingually in allergic rhinoconjunctivitis in a double-blind trial against placebo.

Material and methods

Patients

Fifty-eight patients with pollen rhinitis, associated in 28 cases with conjunctivitis, were accepted for inclusion in this clinical study, which had been approved by the ethics committee of the hospital. All the patients, or parents of the minors, gave their informed consent. The diagnosis of allergy to pollen was made by clinical history, positive skin tests made with a standardized pollen extract (Stallergènes, Fresnes, France), and the presence of specific IgE as shown by RAST (Pharmacia Diagnostics AB, Uppsala, Sweden) with class 3 as a minimum value. Other sensitivities to mites, weeds, trees, and animal epithelia were not exclusion criteria. In case of sensitivity to animal epithelia, the domestic animal could not be present in the family home. The patients were randomly separated into two groups, for placebo or active treatment. Table 1 shows that the

Table 1. Characteristics of patients included in study

	Active treatment	Placebo treatment
Number of subjects	29	29
Male/female	17/12	14/15
Mean age (years) $\pm$ SD	23 $\pm$ 10	27 $\pm$ 12
Age distribution (years)	(13–43)	(13–51)
Mean duration of sensitivity (years) $\pm$ SD	11 $\pm$ 7	10 $\pm$ 6
Sensitivity other than grass	14	13
Previous parenteral desensitization	15	14

characteristics of the two groups of patients were similar when included in mean age, sex, duration of rhinitis, and number of sensitivities other than grass.

Allergen preparation

The same batch of purified, standardized allergen (11) was used throughout the study. Its activity was established as an index of reactivity (IR). A solution is labeled 100 IR when it induces a wheal of a geometric mean of 40 mm² when prick tested in 30 subjects who are sensitive to the corresponding allergen.

Symptom scores

Symptom scores were recorded daily for rhinitis and conjunctivitis. Rhinitis, sneezes, nasal discharge, and nasal obstruction were scored 0–3. Conjunctivitis, eye redness, and itching of eyes and tears were also scored 0–3. A score of 0 indicated absence of signs or symptoms, score 1 signs or symptoms present but not serious, and scores 2 and 3 serious or very severe symptoms.

Medication scores

No therapy was allowed during the study; in particular, long-acting antihistamines and topical or systemic corticosteroids. However, rescue treatment was authorized for insufficiency of effect of desensitization on the symptoms. This treatment was noted daily and was specified according to the following scale:

- minor symptoms of rhinitis: administration of 2% nasal disodium cromoglycate (Fisons, Loughborough, UK)
- minor symptoms of conjunctivitis: administration of drops of 2% disodium cromoglycate (Fisons, Loughborough, UK)
- moderate symptoms: tablets of terfenadine at 120 mg (Marion Merrell Dow)
- in case of failure or setback in the treatment and severe symptoms: tablets of 0.25 mg betamethasone and 2 mg dexchlorpheniramine together (Schering-Plough).

Treatment

Treatment by sublingual drops of five-grass pollen extracts or placebo, in the same glycerol-saline diluent, started 21 February 1991, and the study ended 30 June 1991. The progression of doses was made in 40 days. It started with 1 drop of 1 IR/ml up to 10 drops on day 10, while on days 11–20, 1–10 drops of 10 IR/ml were given. Finally, from days 20–40, the patients took 1–20 drops of 100 IR/ml. Once this dose of 20 drops was reached, maintenance treatment was followed every day for 30 days and then every 2 days for the following 30 days. The cumulative dosage received by the patients was therefore 4500 IR.

Pollen counts

Pollen counts were obtained from the Laboratory of Aerobiology, Pasteur Institute, Paris.

Statistical methods

A nonparametric, one-way analysis of variance, the Kruskal-Wallis H-test, was used to determine a global difference between all groups. When significance was indicated, the two-sample Mann-Whitney U-test was applied. Overall clinical efficacy was assessed by the Cochran Mantel Haenzel test. All values are given as mean (SE). The level of statistical significance was set at 0.05.

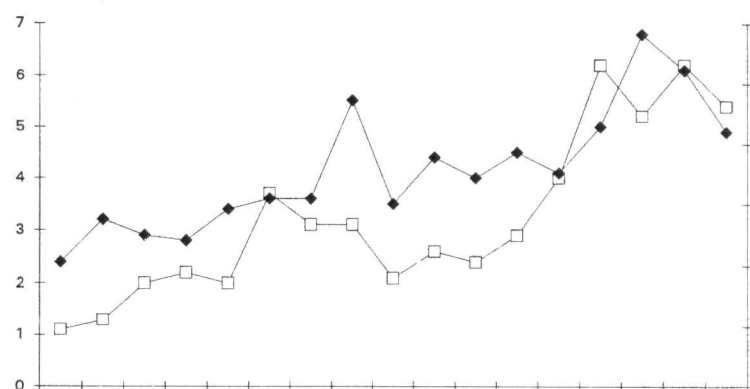
Results

Fig. 1 shows the mean weekly symptom scores for rhinitis for the two groups of patients. It also shows the pollen counts. Fig. 2 shows the same data for conjunctivitis.

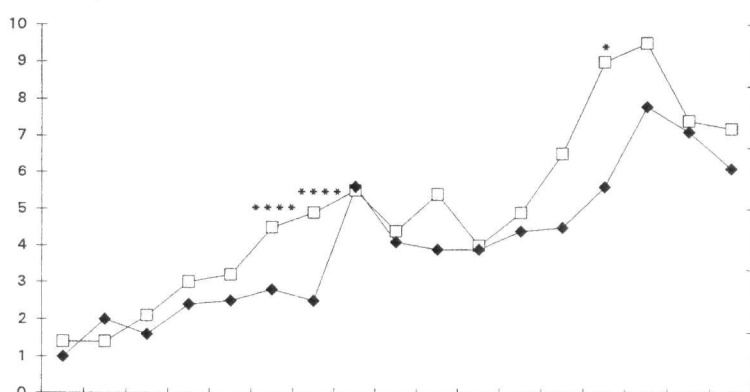
The symptom scores for rhinitis, sneezing, and rhinorrhea increased slightly for weeks 6 and 7, and then much more definitely for the last 5 weeks of the study. These periods coincide with a small early pollen peak, and then the main pollination peak. Comparison of treated and placebo groups shows a significant difference in favor of the treated group for weeks 7, 12, 13, 14, and 15 for sneezing and in weeks 6, 7, and 14 for rhinorrhea. The study of nasal obstruction scores generally showed a nonsignificant tendency for more marked severity in the treated group throughout the study even at base line.

The scores for ocular symptoms showed development that was similar to rhinitis. Comparison of treated and placebo groups showed a significant difference in favor of the treated group for eye redness in weeks 12, 14, and 17 and for tears in weeks 14, 15, and 17. However, similar tendencies observed for ocular pruritis did not become significant.

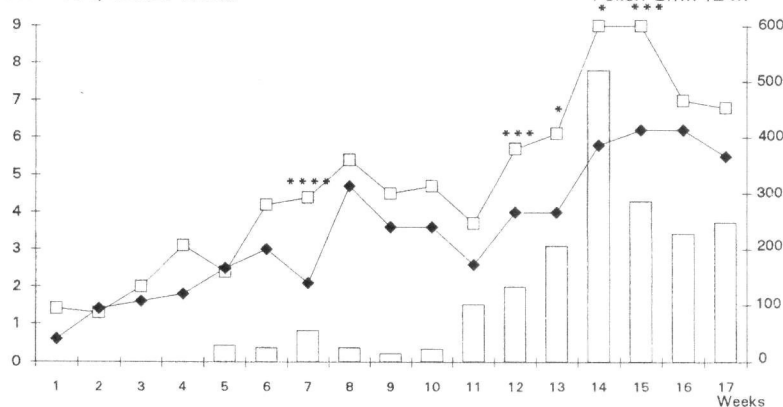
Mean weekly nasal obstruction scores



Mean weekly rhinorrhea scores



Mean weekly sneeze scores

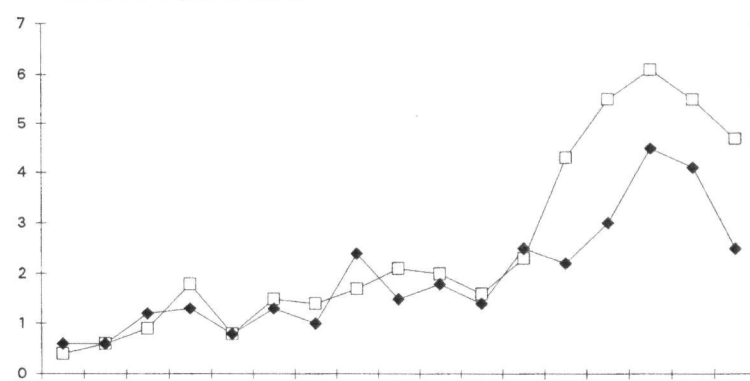


□ Placebo group ◆ Treated group

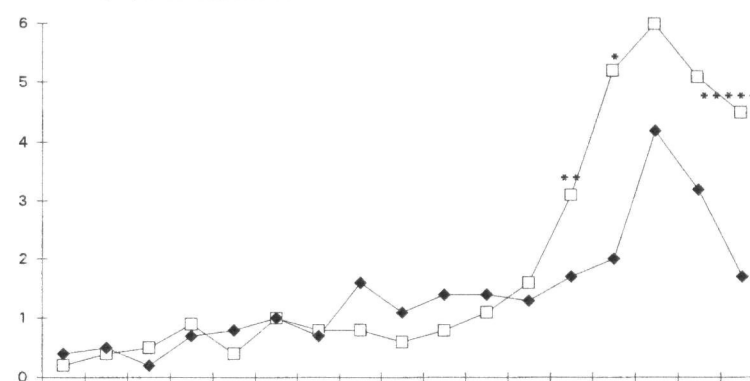
Fig. 1. Mean weekly sneeze, rhinorrhea, and nasal obstruction scores, and pollen counts (* $P < 0.05$; ** $P < 0.04$; *** $P < 0.03$; **** $P < 0.01$).

The results must also be interpreted with reference to medication consumption. Fig. 3 shows that during the period of maximum pollination, consumption of the nasal spray of sodium cromoglycate was significantly less in the desensitized group than in the placebo group. Fig. 3 also shows that medication consumption was similar in the two groups for terfenadine and sodium cromoglycate eye-drops. Finally, it shows that the consumption of betamethasone and dexchlorpheniramine was significantly less in the desensitized group. Overall, betamethasone and dexchlorpheniramine consumption was 77 tablets for weeks 7–18 for the treated group, and 355 tablets for those on placebo. Overall clinical efficacy was assessed by both patients and investigators, with the opinion of the investigators expressed as failures,

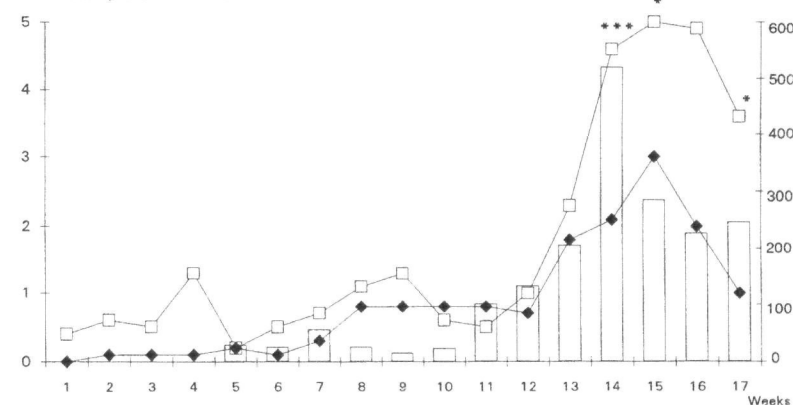
Mean weekly ocular pruritis scores



Mean weekly eye redness scores



Mean weekly tears scores



□ Placebo group ◆ Treated group

Fig. 2. Mean weekly eye redness, tears, and ocular pruritis scores, and pollen counts (* $P < 0.05$; ** $P < 0.04$; *** $P < 0.03$; **** $P < 0.01$).

moderate results, or success. Desensitization seemed to be significantly more efficacious than placebo ($P < 0.04$). At the same time, the opinion of the patients, coded in the same way, indicated a non-significant tendency in favor of the active treatment ($P < 0.16$). With regard to side-effects, the

Table 2. Types and frequencies of side-effects

Side-effects	Placebo group	Treated group
Skin	2	—
Buccopharyngeal pruritis	1	4
Rhinitis	4	5
Digestive signs	1	1
No. of patients	7	10

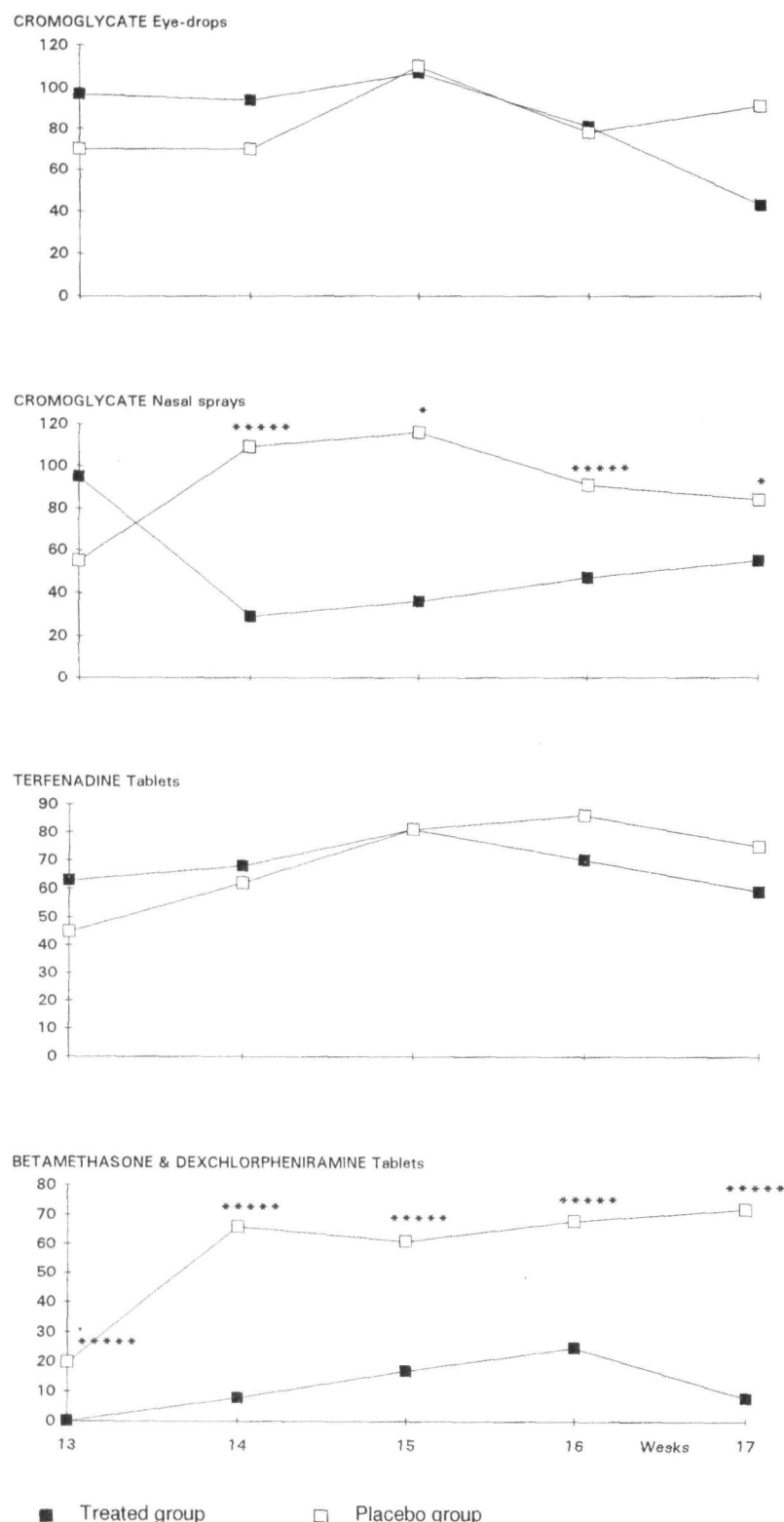


Fig. 3. Consumption of solution of nasal cromoglycate, terfenadine, cromoglycate eye-drops, and betamethasone and dextchlorpheniramine (* $P < 0.05$; ***** $P < 0.01$).

only incidents reported were minor and of doubtful attribution with incidence about the same in both groups, as shown in Table 2.

Discussion

Only four controlled studies report the results of the treatment of allergic rhinitis by sublingual desensitization (15–18). The first, a double-blind, placebo-controlled, crossover trial describes the results of low-dose sublingual therapy with house-dust mite in 18 patients with perennial rhinitis (16). As this study was very brief (15 days) and used low doses near

those of the homeopathic approach, it is difficult to consider it as significant for the efficacy of immunotherapy. The authors themselves suggest a reaction of the “low dose tolerance” type as a possible mechanism of sublingual therapy which reflects subthreshold coating of basophils and mast cells by a dose of antigen which is too low to cause degranulation. Many criticisms have been expressed (1, 19), but this study remains the first controlled study devoted to sublingual therapy.

Another trial was much more significant as it focused on a group of 40 patients with seasonal hay fever over 24 months (18). The cumulative dose of grass-maize pollen extract rose 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. It was noted only that the use of inhaled beclomethasone dipropionate and disodium cromoglycate was discouraged.

The third study assessed the efficacy of sublingual immunotherapy in 58 patients under 12 years of age suffering from asthma and rhinitis, who were positive to mites (17). 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 nasal and respiratory symptom scores was already observed after 12 months of treatment, and it became even greater after 18 months of treatment. The same significant difference between groups was shown in medicine consumption. In the active group, more than half of the patients had a reduction of 20% or more in medicine consumption.

The most recent publication on sublingual immunotherapy is a double-blind, placebo-controlled trial over 105 days with standardized cat extract in 41 patients with cat allergy suffering from rhinoconjunctivitis. The total dose of extract was approximately 4 500 000 allergy units, amounting to 3–10 times the classical subcutaneous dose in 1 year. In this study, high-dose sublingual therapy with cat extract was not more efficient than placebo (histamine) therapy in reducing the symptoms of allergic rhinitis. But it has to be mentioned that this study covers a short period of time, and this favors the placebo effect. Moreover, to assess the efficacy of the treatment, the authors studied the response to exposure in an apartment containing cat dander, a situation which was a challenge test, not a usual clinical situation. Unlike other studies, the drops were taken once daily sublingually and held under the tongue for at least 1 min and then the remaining liquid was expectorated without swallowing. Finally, there was an important and significant difference in IgE-specific anticat levels between the active group and the placebo group, in which they were much lower.

In the present study, we assessed the efficiency of sublingual immunotherapy with drops of five-grass allergen extract. The doses administered to produce a result were 50 times higher than those given subcutaneously for the same period. Study of the scores showed significant differences between the treated and placebo groups for the nasal symptoms involved in sneezing and rhinorrhea. This efficacy, seen in the symptoms, was observed although the rescue treatments were significantly reduced. Nasal obstruction, which is more a symptom of perennial rhinitis than seasonal pollen rhinitis, was, on the contrary, slightly aggravated at the beginning of the treatment. This could perhaps be interpreted as a minor side-effect. In the same way, reduction of ocular symptoms was statistically significant in the treated group for eye redness and tears. For ocular pruritis, the difference was not significant because the patient number was too small. Demonstration of efficacy of desensitization was confirmed by a marked reduction in need for betamethasone, which was the strongest of the authorized drugs. Desensitization by the perlingual route thus reduced the severity of rhinoconjunctivitis from grass pollens. All the observations taken together doubtless explain why the judgment of the investigators on treatment efficacy was more favorable than that of the patients. The investigators take into account not only the symptoms but also the reduction in the need for extra therapy.

These favorable results were obtained without evident side-effects. This recalls another, similar study, with longer treatment and increased doses administered to produce a more marked effect on the symptoms. Increase of dosage was justified because of poor knowledge of the proportion of allergen extract that passes internally across the sublingual mucosae or after swallowing into the digestive tract. The major denaturing effect of the gastric and intestinal secretions on the pollen allergens makes the influence of the swallowed portion very doubtful (9, 13). Moreover, oral immunotherapy by the digestive route has been thought to be effective only when the dose administered is 50–200 times greater than that used for subcutaneous injections (3, 7).

The treatments can be done in the patients' homes after appropriate advice, and this method is particularly economical not only for medical care but also because of professional absenteeism, which is frequent in injection desensitization.

Perlingual desensitization seems to be a simpler, less expensive method which is as efficacious as and safer than the classical methods of desensitization.

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