

Efficacy of grass–maize pollen oral immunotherapy in patients with seasonal hay-fever: a double-blind study

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Summary

Forty patients with a well-documented history of seasonal hay fever and a positive skin-prick test specific to grass pollen, including Bermuda grass and maize pollen (*Zea mays*), were allocated randomly on a double-blind basis to receive either an oral mixed grass–maize pollen extract or a matched placebo during the 1981/1982 grass pollen season. After 12 months the code was broken and patients on placebo were transferred to active therapy while patients on active therapy continued with maintenance therapy for another 12 months during the 1982/1983 grass pollen season. The assessment of the effect of the orally administered grass–maize pollen extract was on the clinical symptoms. During the first year the patients on active therapy had significantly fewer hay fever symptoms during the summer months compared with the placebo group. During the second study year, with all patients on active therapy, both groups had markedly milder symptoms compared with the placebo group. Side-effects were negligible. This study concludes that oral immunotherapy with grass–maize pollen extract in grass pollen-sensitive seasonal hay fever patients is safe and effective.

Introduction

There is conflicting opinion concerning the efficacy of immunotherapy via the oral route. There have been a number of uncontrolled as well as controlled studies indicating that the oral route is effective in desensitizing pollen-allergic patients [1–8]. Conversely, recent controlled trials showed no significant effect from oral grass pollen hyposensitization [9–11].

The present study compared an orally administered aqueous grass–maize pollen extract with a placebo in atopic adults with grass pollen-sensitive seasonal hay fever.

The study period was 24 months over two South African summer seasons, August 1981–July 1983.

Subjects and methods

Patients

Fifty-one young adults, of either sex, living in the city of Bloemfontein with at least one year's history of seasonal hay fever and a positive skin-prick test specific to grass pollens, including Bermuda grass and maize pollen (*Zea mays*) were studied. Patients who had received depot steroids within the previous 3 months, those with significant asthma or allergic rhinitis due to allergens other than the pollens included in the extract, those who had received immunotherapy within the previous 3 years and pregnant women, were excluded from the study. Those patients who were on inhaled therapy, such as beclomethasone dipropionate or disodium cromoglycate, or oral antihistamine during the summer season prior to the commencement of the study, were instructed to not use these during the trial period. Patients were assigned randomly in a double-blind cross-over fashion to either the active therapy (AV1) or placebo group (P1).

Treatment

Treatment consisted of graded courses of an aqueous extract followed by maintenance therapy and commenced in August 1981, well before the onset of the grass pollen season. The oral extract contained a mixture of aqueous extracts of twelve grass pollens (B2 grasses, Bencard, U.K.), plus Bermuda grass pollen and maize pollen in phosphate buffered physiological saline preserved with 0.5% w/v phenol identical to Bencard SDV[®] vaccine (Beechams, U.K.) used for injections. The aqueous extract was graded into three strengths comprising three 10-ml pipette vials: vial 1 containing 1/64 dilution of vial 3, vial 2 containing 1/8 dilution of vial 3 and vial 3 highest allergen concentration. The placebo contained only the phosphate buffered physiological saline solution in identical vials.

Patients received increasing doses from each vial over a 15-day period, starting with one drop from vial 1 and increasing by one drop daily to fifteen drops by the fifteenth day, taken sublingually in the morning before breakfast, the drops being kept in the mouth for at least 1 min and then swallowed. This process was repeated for the second and third vials. The total treatment course was 45 days. Maintenance therapy followed the graduated course and consisted of fifteen drops of vial 3 taken sublingually three times a week on Monday, Wednesday and Friday mornings. The patients on placebo took the buffered solution in the same schedule. Maintenance therapy continued for 12 months over one summer season, after which the code was broken. Patients on placebo (P1) were transferred to active therapy (AV3) starting with the graded treatment course for 45 days followed by maintenance therapy three times a week. Patients on active therapy (AV1) continued with maintenance therapy (AV2). Both groups, AV2 and AV3 continued on active therapy for another 12 months over another summer season.

Assessment

Patients were given diary cards for the entire study period on which daily hay fever symptoms were recorded in four grades (0–3, with 0 indicating no symptoms and 3 severe symptoms). The symptoms recorded were sneeze, discharge, blocked nose, itchy nose, rubbing of the nose and itchy eyes. Patients were reviewed at three 15-day intervals throughout the pre-seasonal treatment period, and monthly during the maintenance period of the first summer season, in particular to identify any side-

Table 1. Characteristics of patients in study

		Active treatment AV1 (<i>n</i> = 19)	Placebo P1 (<i>n</i> = 21)
Sex (male:female)		11:8	15:6
Age (years)	Mean	20	21
	(Range)	(10–30)	(18–51)
Duration of hay fever (years)	Mean	13	18
	(Range)	(2–21)	(5–38)

effects. Thereafter, the patients were assessed at 3-monthly intervals. The use of inhaled therapy, such as beclomethasone dipropionate or disodium cromoglycate, was discouraged, with additional therapy being limited to the occasional use of oral antihistamines. Any additional drug therapy required to control the hay fever symptoms had to be recorded. No pollen counts were done.

For statistical evaluation a Kruskal-Wallis multiple comparison analysis of variance test was used and a *P* value less than 0.05 was considered significant.

The trial was approved by the Ethical Committee of the Faculty of Medicine, University of the Orange Free State, and informed consent was obtained from each patient.

Results

Of the fifty-one patients admitted to the study, forty completed the first year of the study, nineteen patients received the active extract (AV1) and twenty-one patients received placebo (P1). Of the eleven patients who did not complete the first 12 months of the study, seven were on active therapy (AV1) and four on placebo therapy (P1). Of the AV1 group, two moved house, two lost interest, two were called up for military service and one became pregnant. Of the P1 group, one complained of nose bleeds and flu, one had an allergic skin rash, one lost interest and one found the taste of the extract unacceptable. Of the forty patients (AV1 and P1) who completed the first 12 months of the study, thirty-one (AV2 and AV3) completed the second year. Of the nineteen from the AV1 group, fourteen patients continued on active therapy (AV2), while of the twenty-one patients from the P1 group, seventeen were transferred to active therapy (AV3). Of the five patients in group AV2, three moved house and two lost interest. Two

Table 2. Mean monthly hay fever symptom scores per patient

Group	No. patients	Aug.	Sep.	Oct.	Nov.	Dec.	Jan.	Feb.	Mar.	Apr.	May	Jun.	Jul.
1981/1982													
AV1	<i>n</i> = 19	27	26	29	41	34	26	10	8	3	3	8	8
P1	<i>n</i> = 21	22	22	45	65	108	128	61	30	13	3	29	41
1982/1983													
AV2	<i>n</i> = 14	3	5	30	20	63	41	29	22	3	1	28	29
AV3	<i>n</i> = 17	48	40	49	9	39	31	43	26	11	5	0	0

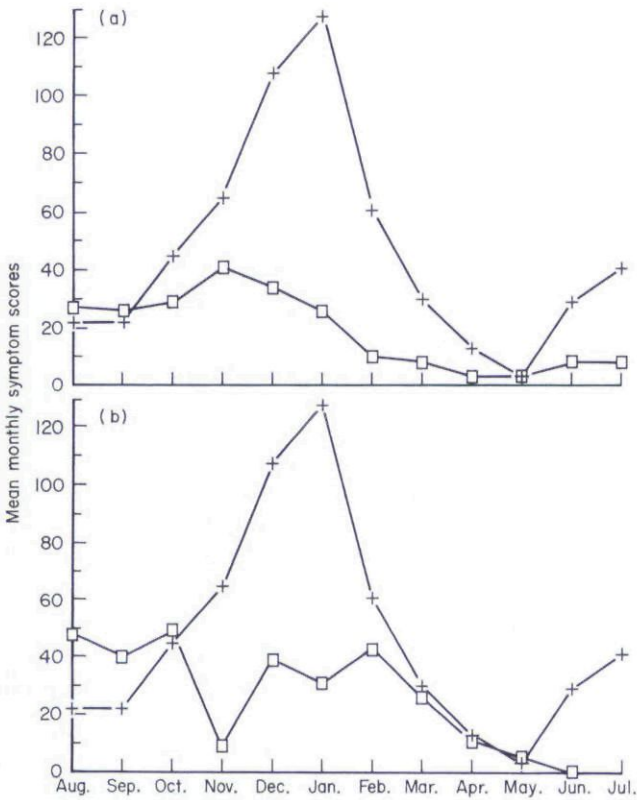


Fig. 1. Mean monthly hay fever symptom scores per patient in (a) the first year (1981/1982) for patients on (□) active therapy (AV1) and (+) placebo (P1); (b) the group on (+) placebo (P1) during 1981/1982 and (□) active therapy (AV3) during 1982/1983.

patients from group AV3 lost interest and two moved house. The patients who withdrew from the study were excluded from the analysis.

Most of the patients in both active and placebo groups had suffered from hay fever for more than 10 years, with a mean duration of 16 years. The duration of hay fever symptoms was not different in the two groups. All patients from both groups had a positive skin-prick test to all three extracts tested, i.e. grasses, bermuda and maize pollen. Their characteristics are given in Table 1.

The response to treatment was assessed using the daily hay fever symptom scores. The sum of the total daily symptom scores was used to calculate the mean monthly symptom score per patient; in the first year for patients on active therapy AV1 and on placebo P1; in the second year for the patients continuing on active therapy AV2, and those commencing active therapy AV3 (Table 2, Fig. 1).

During the height of the first summer season both groups (AV1 and P1), as expected, had an increase in symptoms but a much greater increase occurred in the patients on placebo (P1). During the second study year both groups on active therapy (AV2 and AV3) had an increase in symptoms comparable to the mean monthly symptoms scores of group AV1 during the first study year. The mean monthly symptom scores for AV2 and AV3 were strikingly less than those for P1 during the summer of the first study year. The patients on the active extract had statistically

significant ($P < 0.005$) lower mean monthly symptom scores during the summer months, i.e. October to March. The symptom scores during mid-winter, July and August, were due to acute respiratory infections presenting with a runny, blocked nose, watery eyes and, to a lesser extent, sneezing.

None of the patients on active therapy had any significant side-effects, though most of the patients noted itching of the tongue and lips after taking the drops. These were considered to be mild by all the patients and lasted for only a few minutes. Of the patients who withdrew from the study because of side-effects, two were on placebo. The complaints of the patients were vague and non-specific and were attributed to a lack of compliance. No patient withdrew from the study because of side-effects during the second year of therapy.

Discussion

This study compared an orally administered grass-maize pollen extract with a placebo. Patients were carefully selected as being grass pollen-sensitive with seasonal hay fever symptoms. During the first year of the study those patients on active therapy (AV1) had significantly fewer hay fever symptoms in the summer months than the placebo group (P1). During the second year of the study, with all patient on active therapy, both groups (AV2) and AV3) had markedly lower total mean monthly symptom scores than the symptom scores of the patients on placebo (P1) in the summer months of the first year. The extract was well tolerated and no significant side-effects were encountered.

Both groups (Table 2) had a mean base-line symptom score with symptoms similar to hay fever during the winter months, which is accounted for by intercurrent upper respiratory tract infections that normal individuals are prone to. Strictly seasonal hay fever, where the symptoms are confined to the months of December and January, is uncommon in South Africa. 'Summer' seasonal hay fever generally occurs from late spring to early autumn (October to March). Grass pollen begins to appear in the air in September and October, is at its maximum in December and January, and gradually lessens to disappear in March and April [12].

These results indicate that an oral aqueous extract induced significant clinical improvement in grass pollen-sensitive seasonal hay fever sufferers. It confirms the results of a controlled trial done in Cape Town, South Africa, in which an oral grass pollen extract given to children with seasonal asthma and allergic rhinitis, produced greater relief from symptoms than a placebo [6].

There have been a number of studies indicating that the oral route is effective in desensitizing pollen-allergic patients [1-8]. Many of these studies were done in Europe and most were uncontrolled [1-5]. In controlled trials from Sweden, done on children with rhinoconjunctivitis in which birch pollen extract in enteric coated capsules was compared with a placebo, oral immunotherapy was found to be effective [7, 8].

Other studies of oral immunotherapy in children have failed to demonstrate any clinically significant advantage in oral grass pollen hyposensitization [9-11]. In a recent controlled study of children with pollen-sensitive asthma and rhinitis, oral grass pollen extract was found to have no significant advantage over a placebo [9]. The authors themselves, however, point out a number of other factors that need to be taken into consideration in assessing their results: the matching of the two groups for symptom severity may not have been accurate, the use of medication to control symptoms may

have masked a difference in response between the two groups, and the atypicality of the 1982 pollen season with interspersed high and low pollen counts, and perhaps unusually low antigenic properties of the pollen may have negated the comparative effectiveness of the therapy [9].

In another controlled study of hay fever sufferers, comparing enterosoluble grass pollen tablets with placebo, again no beneficial effect was found from oral immunotherapy [11]. Uncontrolled and inappropriate release of the grass pollen may have been responsible for the lack of effectiveness of the enterosoluble grass pollen tablets, as the site and quantity of active substance released from enteric coated tablets is often unpredictable [13].

Side-effects in this study have been insignificant. This is similar to findings in other studies [5, 6, 9, 11]. Significant gastro-intestinal reactions, i.e. abdominal pain, nausea, vomiting and diarrhoea, have been documented with the use of birch pollen extracts in enteric coated capsules [7, 8]. These symptoms were dose-related and occurred only with high doses of birch allergen extracts.

The surface of South Africa falls into two major physiographic provinces: the large interior plateau and the smaller marginal lands, which lie between the plateau and the coast. The major vegetation of the plateau is part savanna and temperate grassland, with 80% of the vegetation as grass and cultivated harvest, mainly cereals in the latter. The predominant grasses in the Bloemfontein area, which lies in the large plateau, are cocksfoot, meadow fescue, rye grass, meadow grass and Timothy. Bermuda grass is commonly encountered throughout South Africa where it is extensively cultivated as domestic lawn. Little cross-reactivity exists with other grasses [14].

Maize is also extensively cultivated in the region (2·766 and 1·342 million tonne for 1981/1982 and 1982/1983, respectively). It is our clinical experience that exposure to maize pollen will elicit symptoms in seasonal hay fever patients. Many of our patients with seasonal hay fever, and even asthmatics, show positive skin-prick test to maize pollen extracts and not to grasses, while others will have a positive skin-prick tests to grass pollen but not to maize pollen. Little cross-reactivity exists between maize and grasses [14]. As we regard it as an important allergen, it was included in the extract.

As present, oral immunotherapy is not recommended for use in routine clinical practice [9]. Seasonal hay fever, however, is a major problem for many people in South Africa. The symptoms are present mainly during the summer months and are caused chiefly by grass pollen. The country has hot summers, which last for 6–8 months. The long summers are a time of great suffering for pollen-sensitive patients.

In countries with similar long summers, due consideration should be given to the treatment of grass pollen-sensitive seasonal hay fever patients with oral immunotherapy in view of its safety and efficacy. It is particularly desirable in children where the trauma of parenteral immunotherapy may be avoided. In countries with pollen seasons lasting only a few weeks, further investigation as to the optimal dosage of oral extract may be indicated. The advantage and disadvantages of oral immunotherapy must be weighed against the effective and safe medication available for controlling hay fever symptoms.

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