

Clinical and Immunological Effects of Oral Immunotherapy with a Standardized Birch Pollen Extract

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Oral immunotherapy (IT) was evaluated in a pilot study in two centres in children aged 8-15 years with allergic rhinoconjunctivitis. High doses (up to 20×10^6 BU monthly) of a defined freeze-dried birch pollen extract administered in enteric-coated gelatine capsules were given either daily for seven consecutive days every month or once weekly. Symptom scores, as assessed by sneezing, dripping and blockage of the nose, and redness, itching and swelling of the eyes, were significantly lower in treated patients compared to untreated, or placebo treated controls after 3 to 5 months of therapy. In all the 16 treated, but only in three of eight untreated patients, the scores were lower during the pollen season 1982 than during the pollen season preceding the treatment period, despite comparable pollen counts during the two seasons. One year after beginning treatment the reactivity in conjunctival provocation tests was decreased about 10-fold ($P < 0.001$) in the patients receiving more than 2×10^5 BU monthly compared to about two-fold in patients receiving lower doses, or placebo. Increased levels of IgE antibodies directed against birch pollen were recorded in the serum and saliva of most patients after 3-4 months of active IT. In contrast, IgG antibody responses were poor in most of the patients. Side effects, particularly from the gastrointestinal tract, appeared in all treated children. In one of them a systemic reaction occurred during IT. The study indicates that properly performed oral IT with a potent birch allergen extract in enteric-coated capsules may be effective.

Key words: oral immunotherapy; birch pollen allergy.

Accepted for publication 30 December 1985

CLINICAL ASPECTS

The findings that oral IT may be effective provided a high dose of a characterized freeze-dried extract is given in a form that is delivered into the small intestine, warrants further studies. Such therapy could represent several advantages over conventional s.c. IT, e.g. simplicity and lower costs. The gastrointestinal side effects appear to be preventable to some degree, making this form of IT even more attractive.

Several controlled studies have shown that subcutaneous immunotherapy (IT) with allergenic extracts of defined quality and potency is effective in the treatment of allergic rhinoconjunctivitis (5, 7, 11). Uncontrolled studies, particularly from Switzerland and Germany,

have suggested that oral administration of small amounts of allergenic extracts may also be effective (13, 16, 17). This, however, could not be confirmed in four recent controlled studies (2, 12, 14, 15). The lack of effect could possibly be explained by low potency of the extracts used

and by partial digestion of the allergen in the stomach and duodenum. Since well-characterized extracts with defined allergenic potency have been developed in recent years, we decided to investigate in a pilot study, the effect of oral administration of high doses of one such standardized preparation administered in enteric-coated capsules.

MATERIAL AND METHODS

Patients

Twenty-six children (16 boys and 10 girls), aged 8 to 15 years, with seasonal symptoms of rhinoconjunctivitis mainly during the birch pollen season were studied. Allergy to birch pollen was verified by positive skin prick test (SPT) and by positive conjunctival provocation test (CPT). Although not a criterion for inclusion, all children had circulating IgE antibodies against birch pollen as determined by Phadebas RAST® (Pharmacia, Uppsala, Sweden). In addition, some of them had a slight allergy to grass pollen and/or house dust mites, moulds and animal dander, which, however, was considered clinically unimportant. None of them had previously been treated with IT. Of the 26 children 17 were treated at the University Hospital, Umeå (Group A) and nine at the Karolinska Hospital, Stockholm (Group B). Group A consisted of nine children treated in a double blind manner with either active ($n = 5$) or placebo ($n = 4$) capsules, four patients treated openly with active capsules, and four patients who only got symptomatic drugs when they had symptoms. The Group B children were all treated openly.

Allergenic extracts

Pharmalgen®/Spectralgen® birch pollen of the same batch (Pharmacia AB, Uppsala, Sweden) was used throughout the study for SPT and CPT. For IT a crude extract of the same raw material was used. Gelatine capsules were filled with varying amounts of freeze-dried birch pollen extract mixed with lactose. Five strengths

of capsules were made, i.e. 0.015, 0.15, 1.5, 15 and 150 mg pollen extract corresponding to 300 BU – 3 million BU. The placebo capsules were filled with lactose only. The capsules were designed to dissolve about 40 min after passing pylorus.

The same source material as was used in the manufacturing of the capsules was also used in the production of discs in the Phadebas RAST system for determination of IgE antibodies against birch pollen.

Dose schedule

Treatment was started in November 1981 to January 1982, i.e. 4 to 6 months before the leafing season. The initial dose was one capsule (0.015 mg) with 300 BU of birch pollen allergens. The doses were then increased three-fold to 0.045 and 0.15 mg with 4-h intervals. The following days three doses with 4-h intervals were given, increasing the dose three-fold up to 450 mg corresponding to 8–9 million BU, or until side reactions were noted. If no reactions were noted Group A patients in Umeå continued with the maintenance dose daily for 30 days and then for 7 consecutive days every 4 weeks. The Group B patients received the maintenance dose once a week. When reactions of possible allergic nature, e.g. gastrointestinal disturbances occurred, treatment was stopped for 1 week. The patients then received for 3 days one tenth of the dose giving side effects. After that they received a three-fold increase dose for another 3 days and then the original dose for yet another 3 days. Treatment was continued for 1 year with the exception of a 6-week period during the leafing season when no capsules were given.

Symptom scores and symptomatic medication

During the period May 1 – June 10, within which the birch pollen season occurs each year, the patients recorded the symptoms from the nose and eyes, as well as the medication taken. Eight variables were registered every day, i.e. three from the nose (sneezing, dripping, and blockage), three from the eyes (redness, itching

and swelling) and two variables to record night symptoms, i.e. global evaluation of the symptoms from the nose and eyes. A 4-grade scale was employed for the registration, i.e. 0 = no symptoms, 1 = light symptoms, 2 = moderate symptoms and 3 = severe symptoms. The sum of these figures each day represented the daily symptom score, thus giving a maximum of 24 points/day. All daily symptom scores were then added into a total symptom score.

The only medication allowed for Group A patients was clemastine (Tavegil®) in the case of severe rhinoconjunctivitis, while the Group B patients were allowed other symptomatic therapy as well, although excluding systemic or topically applied corticosteroids.

Skin prick tests and conjunctival provocation tests

The SPT were performed in duplicate using Pharmedal freeze-dried allergenic preparation in three concentrations, i.e. 1000, 10,000, 100,000 BU/ml. The CPT were performed according to Möller et al. (10) with increased concentrations of allergen dripped every 20 min into alternate eyes until a positive reaction occurred.

Nasal secretions were sampled as described by Deuschl et al. (3).

Antibody analysis

The IgE antibody levels in serum and nasal secretions were determined employing the Phadebas RAST (Pharmacia Diagnostics AB, Sweden), as recommended by the manufacturer, using commercially available discs. The results were expressed in Phadebas RAST Units (PRU). The IgG antibody levels against birch pollen were determined using a method based on ^{125}I -labelled birch pollen allergen and adsorption of the serum IgG fractions to protein A coupled to Sepharose (14). To compensate for any possible dilution of samples the antibody levels in nasal secretions were related to the levels of human serum albumin in the secretion as determined by single immunodiffusion as described by Johansson et al. (6).

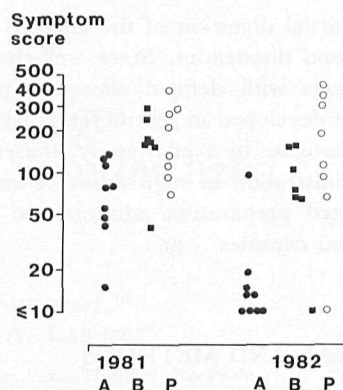


Fig. 1. Symptom scores in 1981 (pretreatment) and 1982 in patients receiving oral IT, placebo, or symptomatic treatment only. Closed circles denote treated patients in Group A, closed squares treated patients in Group B, and open symbols untreated or placebo-treated patients (P).

Pollen counts

Pollen counts were obtained from continuous registration in both the Stockholm and Umeå areas.

Statistical methods

Student's t-test of unpaired observations and chi-square analysis were employed.

RESULTS

All the 16 actively treated patients, in whom symptoms were obtained during the tree pollen season in 1981 and 1982, had lower scores in 1982 after 3–5 months of treatment (Fig. 1). In contrast, reduced symptom scores in 1982 were recorded in only three of the eight untreated, or placebo-treated controls. The difference between the actively treated and the non-treated children was significant ($P < 0.05$).

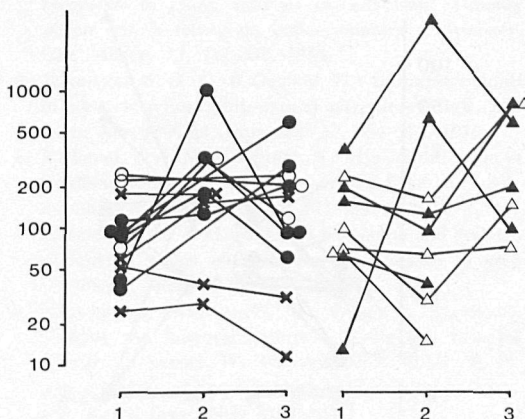
These results should be evaluated in light of the fact that the pollen counts were slightly higher in the spring of 1982 compared with 1981. Thus, the birch pollen season lasted for less than 3 weeks in 1981 in Umeå (Group A), and for 6 weeks in 1982, although the peak values were slightly lower the second year. In Stockholm (Group B) abundant birch pollen,

i.e. more than 100/m³ air, were recorded during 7 days in 1981 and 15 days in 1982. The peak pollen counts for 1 day in Stockholm in the 2 years were 408 and 1235/m³ respectively.

The improvement as assessed by the symptom scores was confirmed by the results of the CPT's performed in October 1982 (Table 1). Compared with the CPT results 1 year earlier, 10 of the 11 patients tested in October 1981 and 1982 and who had received a maintenance IT of at least 0.2×10^6 BU, tolerated higher concentrations of the extract in 1982, seven of them 10 times higher or more. In one patient the sensitivity was unchanged. Of the six patients who only received low allergen doses due to side effects and three patients receiving placebo, and who were tested twice, five had a reduced conjunctival sensitivity in the CPT. Four openly treated patients were not tested in 1982. The mean ($\pm$ SD) log¹⁰ concentration of birch pollen extract giving a positive reaction was 3.41 ($\pm$ 0.63), corresponding to 2600 BU/ml before therapy, and 4.36 ($\pm$ 0.39) corresponding to 26900 BU/ml 1 year later in the patients receiving more than 0.2×10^6 BU/months ($P < 0.001$), i.e. the patients were about 10 times less sensitive (Table 1). As shown in the table there was no significant change in CPT reactivity among the patients receiving lower doses or placebo.

Most of the patients treated with more than 0.2×10^6 BU/month had elevated levels of IgE antibodies in serum (Fig. 2a) and nasal secretions (Fig. 3) against birch pollen allergens after 3–5 months and/or after 1 year of active treatment. The IgG antibody responses in serum were generally less pronounced and more

IgE, PRU



IgG, units

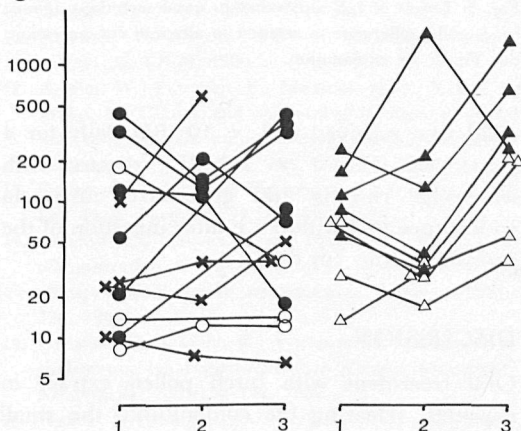


Fig. 2. Serum levels of IgE (2a) and IgG (2b) antibodies against birch pollen before (1), after 3–5 months (2) and after 1 year (3) of therapy. Circles denote treated patients in Group A, triangles Group B. The closed symbols indicate children in whom the monthly maintenance dose was at least 0.2×10^6 BU and open symbols children receiving a lower dose. X denoted placebo-treated patients.

Table 1

The log¹⁰ concentration (mean $\pm$ SD) of birch pollen extract giving a positive CPT in October 1981 (pretreatment) and October 1982

Monthly maintenance dose BU $\times 10^{-6}$	CPT reactivity	
	1981	1982
> 0.2	3.41 $\pm$ 0.63	4.36 $\pm$ 0.39
	n.s.	$P < 0.05$
< 0.2	3.50 $\pm$ 0.71	3.83 $\pm$ 0.50
	n.s.	

than two-fold increase was only recorded in eight of the 18 treated children and in one of the four placebo controls.

All the patients had adverse reactions to the pollen capsules at some time during the treatment, indicating that they all reached their maximum tolerated dose. The reactions were predominantly gastrointestinal, i.e. all the children at some time had diarrhoea, and/or abdominal pain, nausea and vomiting. One

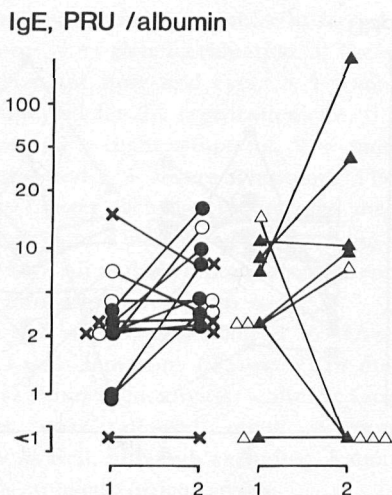


Fig. 3. Levels of IgE antibodies in nasal secretions against birch pollen allergens in relation to albumin concentration. See Fig. 2 for explanation.

child who received $8-9 \times 10^6$ BU daily for 4 days, and then 3×10^6 BU, reacted with wheezing, rhinitis and generalized urticaria which appeared within 1 h after ingestion of the capsule on the 7th day.

DISCUSSION

Oral treatment with birch pollen extract in capsules, releasing the content into the small intestine, induced clinical improvement as indicated by lower symptom scores and decreased sensitivity in CPT. There was also a stimulatory effect on the immune system, as indicated by the IgE antibody responses. The 1982 pollen season which occurred after 3-5 months of therapy, was comparable to the pretreatment season in 1981 with regard to pollen exposure. The similarity in pollen load between the two seasons allows a direct comparison of symptoms in the individual patients.

The study was designed as a two-step pilot investigation. For this reason there were only eight untreated controls, four of whom not having anything but symptomatic treatment and four receiving placebo capsules. It should, however, be pointed out that the four placebo-treated patients were correctly identified by the responsible clinical investigator (C.M.) because

of lack of gastrointestinal reactions, thus invalidating the concept of a truly blind study.

Oral immunotherapy has been used for a number of years, particularly in Switzerland and Germany (13, 16, 17). Although the biological activity of the preparations has not been studied, the doses have probably been small, the extract not characterized, and no precautions have been taken to protect the allergens during the passage through the stomach. Although clinical improvement has been claimed as a result of oral IT, the four controlled studies done, however, indicate that this therapy is not superior to placebo (2, 12, 14, 15). The main difference between the present and previous studies is that we used substantially higher doses of allergenic extracts, reaching a maximum of 450 mg in a single dose, which is equivalent to about $8-9 \times 10^6$ BU. The monthly maintenance dose was up to 20×10^6 BU. This should be compared with the usual maximum dose for subcutaneous IT of 10^5 BU/month or less. Dosage may be a decisive factor.

When comparing different studies of oral immunotherapy it should also be noted that the allergenic activity of pollen is degrading after 10 min in gastric acid (8). Therefore, it seems important that the capsules protect the pollen content well during the passage through the stomach. On the other hand, the pollen should be liberated in the small intestine to stimulate effectively the gut-associated lymphoid tissue. Our capsules fulfilled these demands as indicated by pharmaceutical analysis.

Gastrointestinal and systemic reactions after oral ingestion of pollen have been described previously (15), but in the present study the gastrointestinal reactions were so common, that it is obvious that a less aggressive dose schedule is necessary. One patient even had a systemic reaction. Since the allergens were administered in enteric-coated capsules the systemic reaction was most likely explained by absorption of the allergen through the intestinal mucosa.

There is ample evidence from animal experiments, as well as from human vaccination studies, that orally administered antigen may induce an immune response detectable in vari-

ous mucosal membranes (9). Animal studies have also shown that this route of immunization may lead to an induction of suppression (1). This was not seen in our patients, in whom there was increased IgE and IgG antibody levels in serum. Instillation of allergen extracts in the nose, which may prove to be another effective way of mucosal immunotherapy, also results in stimulation of the local and systemic IgE and IgG antibody production (3).

In conclusion, this pilot study shows that oral IT may be worthwhile, provided high doses of a defined allergen preparation are given and that the immune system in the intestinal mucosa is reached and stimulated.

ACKNOWLEDGEMENT

This work was supported in part by a grant from the Swedish Medical Research Council to S. G. O. Johansson (16X-105)

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