

Oral Immunotherapy of Children with Rhinoconjunctivitis due to Birch Pollen Allergy

A Double Blind Study

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Thirty children with rhinoconjunctivitis due to birch pollinosis were treated in a double blind manner for 10 months with enteric-coated capsules containing either a birch pollen preparation ($n = 14$) with doses up to 1.4×10^6 biologic units per day or placebo ($n = 16$). Compared with the placebo group the actively treated children had less symptoms during the birch pollen season after 3 months of therapy ($P = 0.035$). Skin prick reactions decreased significantly more in the active group than in the placebo group after 10 months ($P = 0.01$). Conjunctival sensitivity was lower in the active group than in the placebo group after 3 months of treatment ($P = 0.01$) but not after 10 months. Compared with the placebo group the treated children more often increased their levels of IgG ($P = 0.007$) and pre-seasonal IgE ($P = 0.001$) against birch. There was a seasonal increase of IgE antibody level against birch in the placebo but not in the treatment group ($P < 0.001$). None of the treated children developed asthma, compared with five of the untreated children. No general reactions occurred and few side effects were seen during the treatment period. We conclude that in children with birch pollinosis oral immunotherapy with high doses of a biologically potent preparation in enteric-coated capsules is effective, easy to perform, economic and safe.

Key words: birch pollen; conjunctival provocation test; IgE; IgG; immunotherapy; oral immunotherapy; skin prick test.

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CLINICAL ASPECTS

Using high doses of the allergen in enteric-coated capsules, oral immunotherapy of birch pollinosis is effective with only moderate side effects in the form of gastrointestinal disturbances. Compared with conventional immunotherapy the oral treatment seems to be simpler, less expensive and associated with a lower risk for general reactions.

Several authors have claimed that oral immunotherapy (OIT) is effective in the treatment of pollen-allergic patients (5, 14, 16, 17, 19, 20), although controlled trials have indicated that this is probably a placebo effect (4, 12, 15, 18). Nevertheless, in a recent study, we pointed out that OIT may be effective in pollen-allergic patients provided high doses of the allergen are allowed to reach the small intestine (2). But in that study all the patients had gastrointestinal side effects and one patient a systemic reaction. The aims of the present study were to eliminate

these side effects through a modification of the treatment, to confirm that OIT is an effective form of immunotherapy and to study in more detail the immune responses during OIT.

MATERIAL AND METHODS

Patients

Thirty-two children with rhinoconjunctivitis due to birch pollinosis were initially chosen to take part in the study at the Allergy Clinic at

the Department of Pediatrics, University Hospital, Umeå, Sweden. The diagnosis of birch pollen allergy was established through a positive case history (rhinoconjunctivitis during the spring pollen season), a positive skin prick test (SPT) with Pharmed® 10,000 biological units (BU)/ml (Pharmacia AB, Uppsala, Sweden) (1) and a positive conjunctival provocation test (CPT) with the same extract (11). Although not a criterion of inclusion, all the children had IgE antibodies against birch pollen of class 2 or more in Phadebas RAST® (Pharmacia). In addition, some patients had a minor sensitivity to other allergens, e.g. grass pollens or animal danders. Children with perennial rhinitis or asthma were excluded, as well as those with severe asthma during the birch pollen season.

The children and their parents were given written and verbal information about the aims and nature of the study, and the parents gave their written consent. The investigation was approved by the Medical Ethics Committee of Umeå University Hospital.

The children were allocated at random to either active treatment or placebo, and the study was performed in a double blind manner. Two children, assigned to receive active treatment, dropped out from the study before the start of the treatment, one not giving a reason, and the other, because the first capsule became lodged in the oesophagus when swallowed. Despite the random allocation the two groups

were well balanced regarding scoring before treatment, age and sex (Table 1).

Allergen preparations

The same batch of purified, freeze-dried and biologically standardized birch pollen preparation was used for SPT and CPT throughout the study (Pharmed®; Pharmacia).

Enteric-coated gelatine capsules for OIT were designed to dissolve in the small intestine after leaving the stomach. The active capsules were filled with a known quantity of a crude birch pollen extract similar in composition to the Pharmed preparation used for SPT and CPT, and with varying amounts of lactose. The placebo capsules were filled with lactose only.

Skin prick test

Skin prick tests were performed with three concentrations (1000, 10,000 and 100,000 BU/ml) in duplicates in October or November 1982 and 1983, i.e. before and after 10 months of treatment. The geometric mean of the areas in mm² obtained for each concentration was determined. The 10-logarithms of the values were calculated. The mean of the three transformed figures was computed and used for comparison between the two testing occasions.

Conjunctival provocation test

Conjunctival provocation tests were performed in October or November 1982, i.e. before treatment, in April 1983, i.e. after 3 months of treatment immediately before the season, and in October or November 1983, i.e. after 10 months of treatment. The initial strength was 100 BU/ml followed by 320, 1000, 3200, etc. up to 320,000 BU/ml as previously described (11).

Blood samples

Blood was drawn on five occasions, i.e. before treatment, after 1 month and 3 months of treatment, immediately after the season, and after 10 months of OIT. The samples were kept frozen at -20°C until analysed. Specific IgE

Table 1
Patient characteristics before therapy

	Active treatment	Placebo treatment
No. patients	14	16
Sex (M/F)	8/6	8/8
Years of age, range (mean)	8.8-16.8 (13.1)	10.4-15.6 (13.4)
Mean symptom score (points)	15.1	15.6
CPT (BU/ml)*	5900	6400
SPT (mm ²)**	22	20

* The lowest concentration giving a positive reaction (mean for 10log transformed concentrations).

** Mean area for the three tested concentrations (10log transformed values for the areas used for calculations).

antibodies against birch were determined with Phadebas RAST® (Pharmacia) according to the manufacturer's instructions and expressed in Phadebas RAST units (PRU). All samples were investigated in the same run in duplicate.

To calculate levels of specific IgG antibodies, a similar system was used (Phadebas IgG RAST® prototype, Pharmacia) with specially prepared birch allergen discs and anti-IgG-¹²⁵I antibodies. The counts obtained from the gamma counter were compared with a reference curve constructed for each occasion, using serial dilutions of a reference serum. Birch-specific IgG was expressed in arbitrary units/ml (U/ml). In this way values between 20 and 1000 U/ml could be determined. All samples were investigated on the same day in duplicate by the same person.

The general safety of the allergen preparation was evaluated by measuring levels of various components of blood and urine samples obtained on three occasions; i.e. before treatment, and after 3 and 10 months of therapy (Table 2).

Symptom scores

During the pretreatment season in 1982, all children participated in another study and were given medication continuously with clemastine

(Tavegyl®) or astemizole (Hismanal®) from April 30 to June 10 1982, which covered the main pollen season (10). They recorded their symptoms of rhinoconjunctivitis daily using a 4-grade scale: no symptoms (0), mild symptoms (1), moderate symptoms (2) or severe symptoms (3). All figures were added to a total symptom score. Since the capacity of astemizole to ameliorate hay fever symptoms was similar to that of clemastine the use of the drugs did not add to the symptom scores (10).

The only medications allowed during 1983 were clemastine in the case of hayfever and salbutamol (Ventoline®) in the case of asthma. A similar protocol as that used in 1982 was used with the exception that symptoms from the eyes and the nose were recorded separately. Symptoms of asthma and medication levels were also noted. The sum of the scores from the eyes and nose was increased by one point for days when clemastine was used, and this total sum of maximum seven points represented the daily symptom score. Seven consecutive daily symptom scores were added to a weekly symptom score. In this way 6 full weeks (1-6) were obtained.

Treatment

The ambulatory treatment with pollen or placebo capsules started in January or February 1983. Starting with 140 BU (0.015 mg) the doses were increased up to a maximum of 1.4×10^6 BU, or until side effects occurred (Table 3). Thereafter, the maximal tolerated dose was given for 7 consecutive days every 4 weeks, aiming continuously for higher amounts up to 1.4×10^6 BU. No capsules were to be taken

Table 2

Haematological and urinary test data obtained from the children before, after 3 months and after 10 months of OIT

Haematology:

Haemoglobin, haematocrite, total red blood cells, reticulocytes, total white blood cells, eosinophils, platelets (in whole blood).

Electrolytes:

Sodium, potassium, chlorides, calcium, protein correlated calcium, phosphorus (in serum).

Liver function:

Total bilirubin, direct reacting bilirubin, alkaline phosphatase, albumin, glutamine acid-acetic acid transaminase, glutamine acid-acid transaminase, lactate dehydrogenase (in serum).

Kidney function:

Creatinine, CO (in plasma), pH, protein, glucose, acids, red blood cells, white blood cells (in urine).

Table 3

Dosage of pollen capsules

Day No.	Dose (BU)
1	140 + 420
2	1400 + 4200
3-9	1.4×10^4
10-16	4.2×10^4
11-23	1.4×10^5
24-30	4.2×10^5
31-37	1.4×10^6

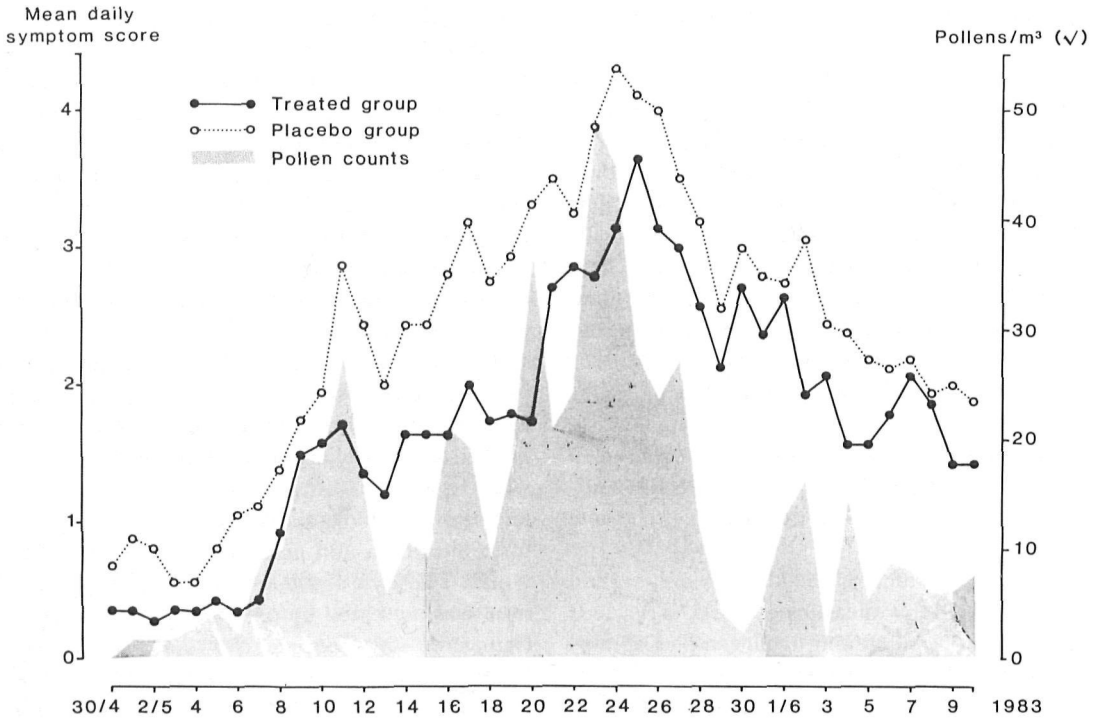


Fig. 1. Mean daily symptom scores and pollen counts.

from May 7 to June 15, i.e. during the most intense pollens season. The dosage and side effects were registered daily. To control that the capsules were taken as planned the registrations were examined after each treatment period of 7 days.

Pollen counting

To obtain daily pollen counts during the scoring period 1982 and 1983, pollens were collected with a Burkard volumetric trap placed on the roof of a 25 m high building in an elevated part of the town.

Statistical methods

For comparison of symptoms in relation to pollen counts a dynamic model was used by which it was possible to evaluate the instant effects of a pollen peak on symptom scores and the duration of symptoms. The model for this study can be expressed as:

$$Y_{ki}(t) = \mu + \alpha_{ki} + \beta_0 Y_{ki}(t-1) + (\beta_1 - \beta_0) k Y_{ki}(t-1) + \gamma_0 P(t) + (\gamma_1 - \gamma_0) k P(t) + \varepsilon_{ki}(t)$$

where

$Y_{ki}(t)$ = symptom score for patient No. i , day t , in treatment group k ,
 $i = 1, \dots, n$, $t = 1, \dots, 42$,
 $k = 0$ (placebo group) or 1 (actively treated group).

μ = overall average symptom score

α_{ki} = individual variation

β_{ki} = decline rate

γ_{ki} = instant impulse response

$P(t)$ = pollen counts (square root transformed)

$\varepsilon_{ki}(t)$ = independently and identically distributed random errors with zero means.

The model is described in detail elsewhere (3).

Comparisons between the groups regarding changes in CPT, IgG, and IgE antibodies, were

Mean weekly score

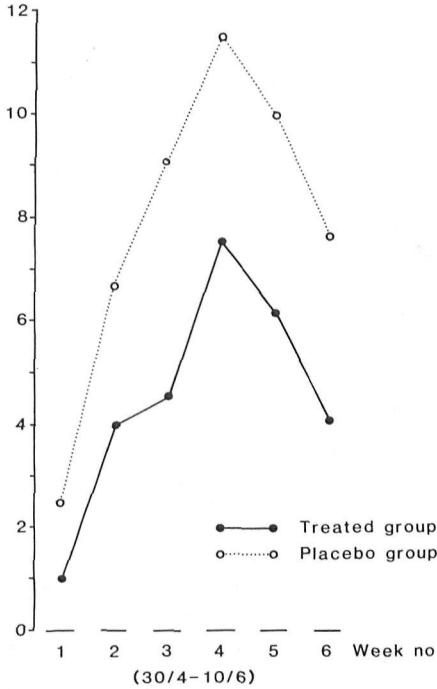


Fig. 2a. Nasal scores.

Mean weekly clemastine consumption (mg)

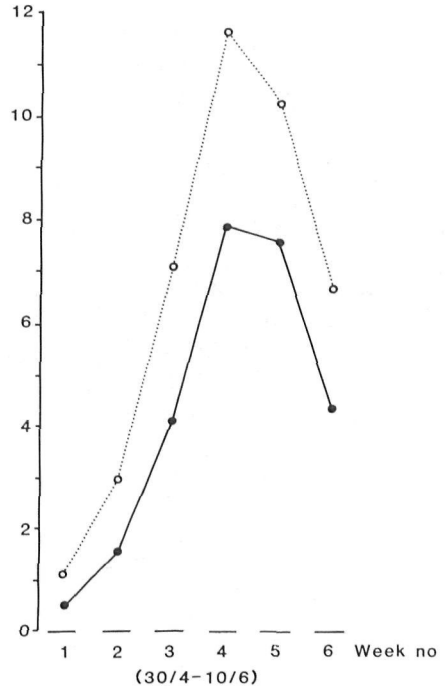


Fig. 2c. Antihistamine consumption.

Mean weekly score

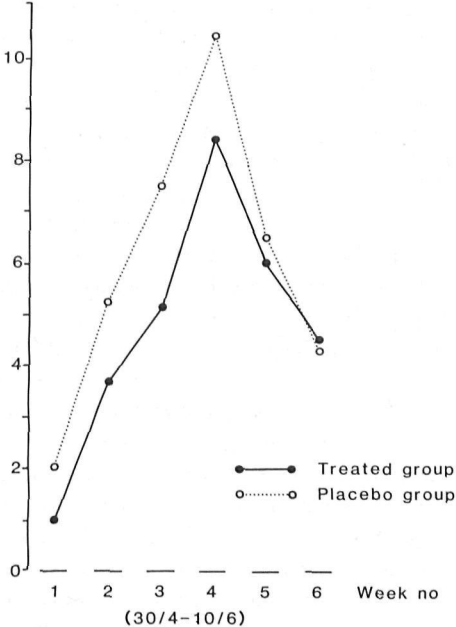


Fig. 2b. Ocular scores.

done with chi-square test (with Yate's correction), and changes in SPT, weekly clemastine consumption, and weekly scores for eye symptoms and nose symptoms, with Student's *t* test. Correlations were analysed with Spearman's correlation coefficient. All tests were two-tailed.

RESULTS

Mean daily symptom scores for the two groups with the corresponding pollen counts from deciduous trees (mainly birch pollen) during the spring 1983 are shown in Fig. 1. The OIT group had significantly lower scores than the placebo group ($P = 0.035$). This was due to the placebo group responding to every pollen peak with higher symptom scores than the actively treated group. The time for the symptoms to disappear after these peaks was similar.

The mean weekly scores for eye symptoms, nose symptoms, and clemastine consumption, are visualized separately in Fig. 2 a-c. The

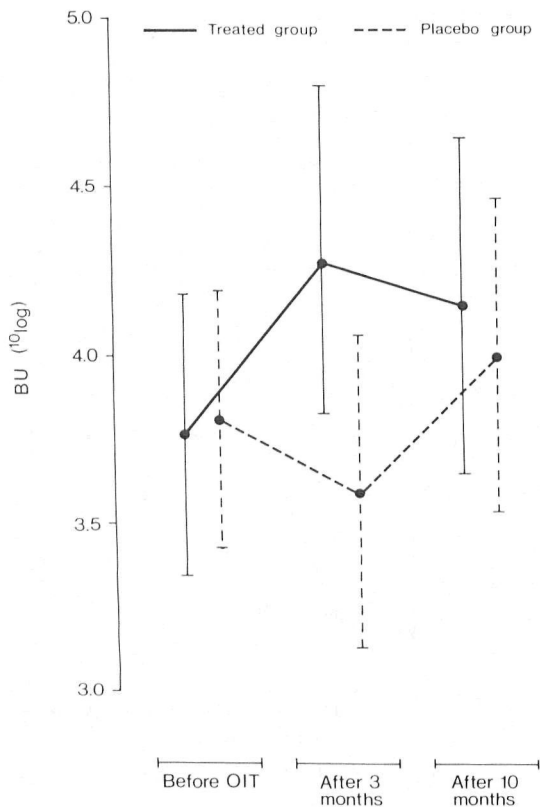


Fig. 3. Conjunctival provocation test. The $^{10}\log$ of the lowest concentration giving a positive reaction is used for calculation of mean and standard deviation.

difference between the groups was statistically significant only for nose symptoms during the 3rd week ($P = 0.007$).

The two groups had similar CPT sensitivity before treatment. After 3 months of OIT, i.e. in April 1983 the actively treated children were less sensitive than those in the placebo group. The number of children with decreased sensitivity was significantly higher in the active group than in the placebo group ($P = 0.01$) (Fig. 3). However, there was no significant difference between the two groups when the third CPT was performed in October 1983. The skin sensitivity as measured by SPT decreased in the active group, i.e. the mean area of the tested concentrations ($^{10}\log$ transformed values) decreased from 22 mm² to 7 mm² 1 year later, i.e. after 10 months of treat-

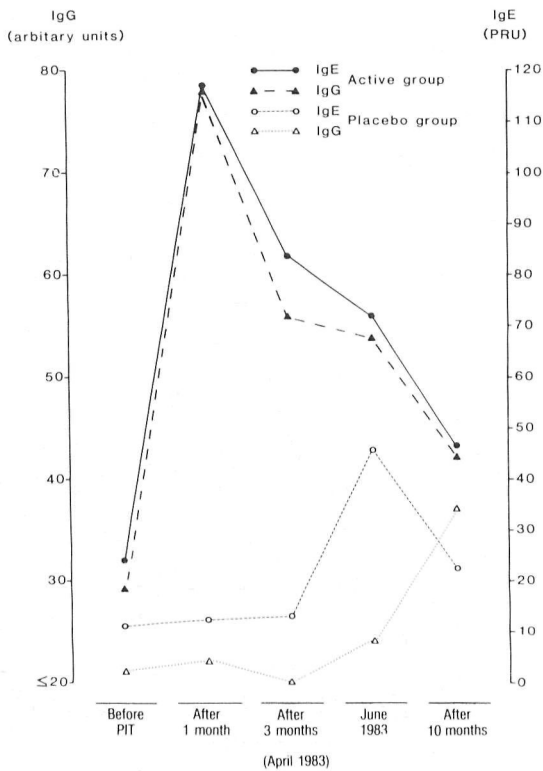


Fig. 4. Birch-specific IgE and IgG (median).

ment. The difference from the placebo group was significant ($P = 0.01$).

During the first 3 months of treatment, i.e. before the pollen season, the level of IgE antibodies against birch increased by more than 100 % in 11 of the 14 treated children but in only two of the 16 untreated children ($P = 0.001$). In contrast, during the season IgE antibodies against birch increased in 10 children in the placebo group (total 12 children) but in none of the children in the treated group (total 12 children) ($P < 0.001$; Figs. 4, 5a and 5b).

The changes in birch-specific IgG antibody levels were moderate, but an increase of at least 50 % during the first 3 months of treatment was seen in eight of the actively treated children compared to only one in the placebo group ($P = 0.007$). During the birch pollen season and thereafter, the placebo treated children increased their IgG levels too, but not significantly more than the treated children (Fig. 4).

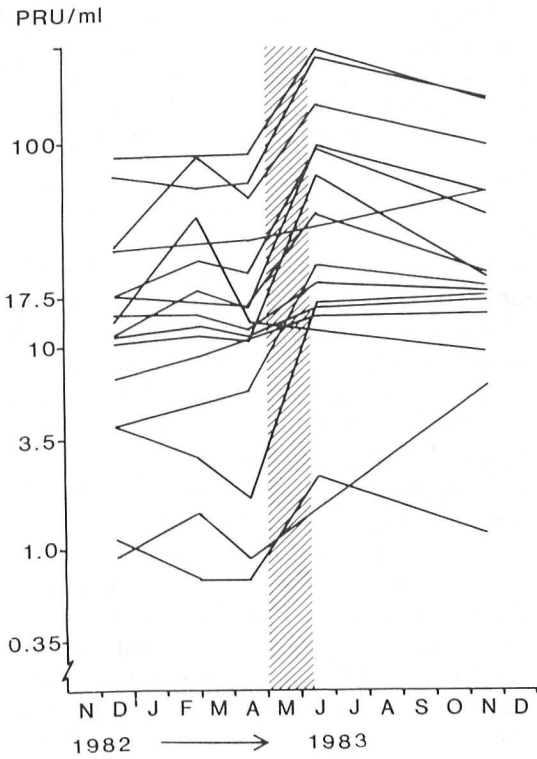


Fig. 5a. Birch-specific IgE in the placebo group.

There was a significant correlation between pre-seasonal CPT results and seasonal eye score in the placebo but not in the treated group, i.e. a low sensitivity in the eye, as measured with CPT, was associated with low eye symptom scores ($r = 0.6$; $P = 0.03$). In the placebo group, but not in the treated group, high IgG antibody levels before, as well as after the season, correlated to high symptom scores. The correlation coefficients were before treatment 0.5 ($P = 0.02$), after 1 month 0.3 ($P = 0.2$), after 3 months 0.6 ($P = 0.008$), immediately after the season 0.6 ($P = 0.01$), and after 10 months 0.6 ($P = 0.01$). In neither group was there any significant correlation between IgE antibody levels and symptom scores.

Occasional haematological and urinary values were outside the normal limits. This was noted in samples before as well as during OIT. There were no significant differences between the two study groups.

The only noted side effects were minor gas-

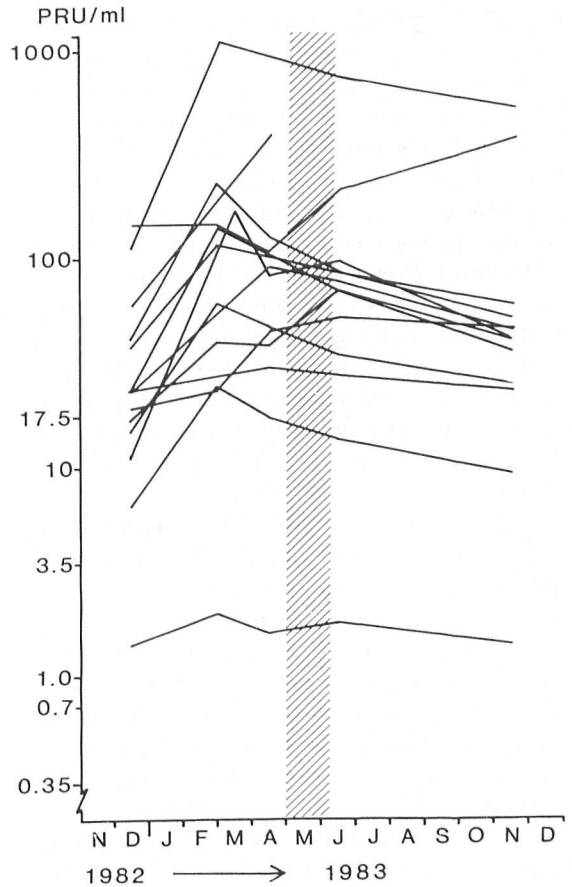


Fig. 5b. Birch-specific IgE in the treatment group.

trointestinal disturbances recorded as nausea, abdominal colic, or diarrhoea. Despite the fact that all but three of the 14 children who received birch pollen recorded gastrointestinal side effects and that these reactions appeared to be of the immediate type, it was not possible to distinguish them from the side effects noted by the children receiving placebo capsules, since similar reactions were recorded in some placebo-treated children. No systemic reactions were seen.

DISCUSSION

Oral immunotherapy, in the form of enteric-coated capsules containing a birch pollen preparation in a weekly dose up to 80 times greater than that used for subcutaneous immuno-

therapy, was found to be an effective form of treatment. Compared to placebo treatment, patients given active treatment showed lower symptom scores, conjunctival sensitivity and skin sensitivity. There was no difference in symptom scores between the two groups before OIT, but the treated group had lower scores than the placebo group throughout the scoring period 1983. Since pollens from deciduous trees cross-react during immunotherapy (9) it is unlikely that the alder season before the scoring period had given an imbalance between the groups. There were also significant differences in specific IgE and IgG antibody responses between those actively treated and children receiving placebo.

The interpretation of the CPT results is difficult. Although a difference in CPT was found already after 3 months of therapy, there was no significant difference between the two groups after 10 months of OIT. Reasons for this remain unknown but could include presence of occasional alder pollens stimulating the placebo group more than the actively treated patients in April, and that the conjunctival sensitivity was less after 3 months of IT than after 1 year, as seen in other studies (7; Möller et al.: Cross-reactivity between deciduous trees during immunotherapy. II. *In vitro* results. To be published).

The lack of seasonal increase in specific IgE antibody levels in the treatment group in contrast to the placebo group is similar to the findings in studies of the effect of subcutaneous immunotherapy (7, 8, 13) indicating an effect of OIT.

Another indication of the treatment effect was the fact that none of the actively treated patients developed lung symptoms, while as many as five of the placebo-treated children acquired asthma during the season 1983, which was an extremely pollen-rich spring. Thus OIT would appear to have protected against the development of asthma during the observation period (6).

In a previous pilot study of OIT we recorded gastrointestinal side effects in all patients and systemic in some (2). Using a modified dose schedule the side effects in the present study

were much less pronounced, consisting only of mild gastric pain and slight diarrhoea. Although 80 % of the treated children had gastrointestinal disturbances these symptoms were not distinguishable from those in the placebo-treated children.

No toxicity of the birch pollen capsules was recorded. The entire treatment was done by the children in their homes. Besides careful instruction, therefore, little effort was required from the hospital staff compared to conventional immunotherapy. Since the treatment was not given in the doctor's office, the patients did not miss school or work, and ensuing transport expenses to the hospital were minimized, OIT would appear to be an inexpensive and safe form of immunotherapy.

In conclusion, this study confirms and extends our previous pilot study that oral administration of high doses of allergen extracts in enteric-coated capsules represents a potentially valuable tool for immunotherapy and shows that side effects can be reduced by proper dose schedules.

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