

Oral immunotherapy in birch pollen hay fever

Ebbe Taudorf, M.D.*, Lars C. Laursen, M.D.*, Åke Lanner, B.S.,***

Bengt Björkstén, M.D.,** Sten Dreborg, M.D.,**.***

Mogens Søbørg, M.D.,**** and Bent Weeke, M.D.*

Copenhagen and Hillerød, Denmark, and Linköping and Uppsala, Sweden

Previous controlled trials with oral administration of allergen have not demonstrated any treatment effect in patients with allergic rhinoconjunctivitis or asthma. In the present double-blind, placebo-controlled trial, we have tested the effect of oral immunotherapy in adult patients with birch pollinosis. Thirty-nine patients completed this 18-month study comprising two birch pollen seasons. The patients received enterosoluble capsules daily, and the actively treated patients reached a cumulated dose of 280 times 10^6 biologic units of birch pollen extract, which is about 200 times higher than the dose used in conventional subcutaneous immunotherapy. We found a significant decrease in eye symptom scores and conjunctival sensitivity to birch pollen, as determined by conjunctival provocation test, as well as a numerical but nonsignificant decrease in nasal symptom scores, nasal sensitivity as determined by nasal provocation test, and antiallergic medication. The treatment was safe, and only a few slight side effects were observed. We thus conclude that our study demonstrates a clinical effect of oral immunotherapy in birch pollinosis. (J ALLERGY CLIN IMMUNOL 1987;80:153-61.)

During the last 80 years, several articles have been published claiming a treatment effect of OIT with various allergen sources in the management of allergic diseases, e.g., rhinoconjunctivitis, asthma, eczema, and gastrointestinal allergy¹⁻⁷; however, only a few of these studies were double-blind and placebo-controlled. None of the studies demonstrated any beneficial effect of oral administration of allergen to allergic patients.⁸⁻¹¹

In this randomized, double-blind, placebo-controlled trial on OIT with enterosoluble birch-pollen capsules in patients with birch pollen-allergic rhinoconjunctivitis, we tested whether OIT has any beneficial effect demonstrable by reduction in eye and nose symptoms and reduced sensitivity in the shock organs measured by CPT/NPT. We have used higher cumulative allergen doses than in previous studies published.

From the *Allergy Unit, Medical Department TTA, State University Hospital, Copenhagen, Denmark, **Paediatric Department, University Hospital, Linköping, Sweden, ***Pharmacia AB, Allergy and Diagnostic Division, Uppsala, Sweden, and ****Medical Department B, County Hospital, Hillerød, Denmark.

Presented at the XII International Congress of Allergology and Clinical Immunology, Washington D. C., October 1985.

Received for publication Sept. 2, 1986.

Accepted for publication Jan. 24, 1987.

Reprint requests: E. Taudorf, M.D., Bakkehusene 2, DK-2970 Hørsholm, Denmark.

Abbreviations used

BU:	Biologic units
CPT:	Conjunctival provocation test
IT:	Immunotherapy
NPT:	Nasal provocation test
OIT:	Oral immunotherapy
SPT:	Skin prick test

MATERIAL AND METHODS

Design

The study started in January 1983, and the first part ended in June 1984, thus covering two birch-pollen seasons (Table I). During their first visit to the clinic, the patients received an SPT with birch Pharmedin (Pharmacia, Uppsala, Sweden), and NPT was carried out. Blood was collected for analysis of birch-specific IgE, IgG, and IgA antibodies, as well as for determination of hemoglobin, white cell and differential counts, and blood chemistry including Na, K, Ca, Cl, HCO_3 , serum proteins, creatinine, alanine transaminase, alkaline phosphatase, and bilirubin. Urine analyses included the determination of glucose, blood, protein, ketones, and pH.

The patients were instructed to record their daily symptoms in the eyes, nose, and lungs, as well as any gastrointestinal side effects during OIT. Two weeks after the first visit, CPT and a second SPT were performed (including alder, elm, and hazel). Each SPT with birch was followed by SPT with alder, elm, and hazel 2 weeks later. During the periods when both NPT and CPT were performed, NPT

TABLE I. Events during the trial

	1983											
	Jan	Feb	March	April	May	June	July	Aug	Sept	Oct	Nov	Dec
Clinic visits	X	X	X	X		X			X	X		
SPT												
Birch	X		X									
Other trees		X		X								
NPT	X		X									
CPT		X		X						X		
Blood tests												
Immunologic	X		X			X			X			
Hematologic	X											
Urine tests	X											
Symptom and medication scores												
Daily capsule intake												
Registration of GI and other side effects												
Collection of tears and sputum												

GI = gastrointestinal; (X) = only half of the patients in each group were having this performed.

TABLE II

Symptom score	Eyes	Nose	Lungs
0 = none	No symptoms	No symptoms	No symptoms
1 = mild	Slight itching	Slight blocking, slight running, no more than five sneezing events per day	A few cases of difficulty in breathing per day
2 = moderate	Some conjunctival swelling, moderate itching, and running	Half blocking, running for more than 3 hours but not all day, from 5 to 15 sneezing events per day	Many cases of difficulty in breathing per day
3 = severe	Strong swelling, itching, and running	Total blocking most of the day, constant running, more than 15 sneezing events per day	Constant difficulty in breathing

was always performed 2 weeks before CPT. In 10 placebo-treated and 10 actively treated patients, tears and sputum samples were collected three times during the trial period for analysis of IgA (tears and sputum), IgG, and IgE antibodies against birch pollen (sputum only).

Patients

Forty-three patients (24 men and 19 women), aged 16 to 47 years, presenting with a history suggestive of birch pollinosis with or without asthma were included in the study according to the following criteria: a positive SPT with 10,000 BU/ml, with Pharmedgen birch-pollen preparation, and a positive NPT and/or CPT at 10,000 BU/ml or less, performed with the same extract. All patients lived within a radius of 60 km from Copenhagen.

None of the patients had received subcutaneous IT with birch-pollen extract before the study, and none had used

systemic corticosteroids. During the trial, none of the patients were pregnant or receiving subcutaneous IT.

The patients that were included were randomized to OIT with active or placebo enterosoluble capsules. Randomization was stratified according to two criteria: the duration of symptoms during the tree pollen seasons and NPT, or, in the case of mainly conjunctival symptoms, CPT. Patients exclusively sensitive to birch pollen had a short period of symptoms, i.e., from the end of April to the beginning of June. Patients sensitive to other tree pollens as well had a long period of symptoms, often starting in the beginning of March. None of the early tree pollens (alder and hazel) contributed significantly to the pollen counts during the birch-pollen season 1983 and 1984. Accordingly, 20 patients were randomized to the actively treated group, and 23 patients were randomized to the placebo-treated group.

Within the first 6 months after randomization, four pa-

Oral immunotherapy

Identical capsules containing either placebo or birch-pollen extract (intermediate product) were manufactured in different colors for each strength: 70 BU, 700 BU, 7000 BU, 70,000 BU, and 600,000 BU. The capsules were enteric-coated in order to pass through the stomach undissolved. Treatment started around February 1, 1983. The capsules were taken with 100 ml of water on an empty stomach, 15 to 20 minutes before breakfast every day. Seventy and 700 BU, respectively, were administered in the first two doses. The dose was then increased approximately threefold once a week (6,800 BU, 20,400 BU, and 68,200 BU) up to a maintenance dose of 2.1×10^5 BU, daily, until mid-May 1983, when the maintenance dose was increased to 6×10^5 daily, which was administered until mid-December 1983. To equalize the basic circumstances for the two testing occasions, January 1983 and January 1984, no treatment was administered for 1 month before the NPT. Two weeks after the NPT (when CPT was performed), treatment was continued with 7×10^4 BU, for 7 days, 6×10^5 BU, for another 7 days, and then a further increase to a new maintenance dose reaching 1.2×10^6 BU, daily, until June 1, 1984. The cumulative dose was approximately 280×10^6 BU.

In the case of severe stomach pain and/or watery stools two or more times per day, patients were informed both orally and in writing to stop taking capsules for 1 week. Thereafter, they took the previously tolerated dose for 2 weeks and then increasing doses according to the recommended dose schedule. In the case of unexplained hay fever, asthma, urticaria, or fatigue, patients were instructed to call the clinic and to stop medication until further instructions were received. The number of capsules and their code was recorded on a special dosage/side effect diary card.

Symptom, medication, and side effect scores

The daily symptom scores were recorded in a 4-grade scale. The score index was printed on the back of the monthly diary cards (Table II).

To control allergic symptoms, the following medication was allowed when it was needed: antihistamine eye and nose drops antazoline and naphazoline (Antistine and Privine; Ciba-Geigy Corp., Summit, N.J.), two drops in each nostril, maximum, three times a day, and antazolin and naphazolin (Antistine and Privine, Dispersa AG, Winterthur, Switzerland), one drop in each eye, maximum, three times a day. If symptoms were not reduced, prednisone tablets, 5 to 10 mg/day were administered. The few patients also suffering from pollen asthma were instructed to take salbutamol/terbutaline aerosol. Theophylline and terbutaline tablets were also allowed. In order to compare the treatment groups, a scoring system was used providing an overall medication score for each day: antihistamine eye drops, one drop = 2 points; antihistamine nose drops, one drop = 1 point; and prednisone, 5 mg per tablet, one tablet = 6 points.

All antiallergic medication allowed for use during the trial period was delivered free of charge from the clinic.

1984					
Jan	Feb	March	April	May	June
X	X	(X)		(X)	X
X					X
	X				
X					
	X				
X					X
X					
X					
(X)	(X)			(X)	

tients were withdrawn, two because of abdominal pain (one after each treatment), one after moving to another geographic region, and one because of poor cooperation. Eventually, the actively treated group was comprised of 11 women and seven men (median age 35 years, range 16 to 45 years), whereas the placebo-treated group consisted of 12 women and nine men (median age 30 years, range 16 to 47 years). In the statistical analyses of symptom and medication scores, another three patients were excluded because of erroneous registration of symptom and/or medication score during the 1984 birch-pollen season. This did not change the group median and range. Sixteen patients in the actively treated group and 19 in the placebo-treated group were allergic/intolerant to hazel nuts and/or one or more of the following food items: apple, tomato, banana, carrot, orange, peach, and pea. At the end of the trial, all patients were asked whether the food allergy had improved, was unchanged, or had deteriorated.

The trial was designed and conducted in accordance with the second declaration of Helsinki. Informed consent was obtained, and the protocol was submitted to the regional ethical committee.

Allergen preparations for diagnosis

The same batches of purified, characterized, biologically standardized, and freeze-dried birch, alder, and hazel pollen-allergen preparations, 100,000 BU/ml (Pharmalgen, Pharmacia),¹² and crude freeze-dried elm allergen extract, 1:45 w/v (Pharmacia), were used throughout the study. The freeze-dried allergens were stored at -20°C until they were reconstituted. The same batch of albumin diluent (0.3 mg/ml of human serum albumin and 0.4% of phenol) was used for all test occasions. The pollen extract was only used for 1 week for SPT and for only 7 hours for CPT and NPT.

TABLE III. Pollen-count levels (grain per cubic meter) for low, medium, and high pollen groups 1983 and 1984

		1983	1984
Low	Median	1	9
	Range	0-4	1-54
	No. of days	11	10
Medium	Median	12	125
	Range	5-19	65-225
	No. of days	11	11
High	Median	55	442
	Range	21-1073	235-973
	No. of days	11	10
All groups together	Overall median	12	125

The medication names were printed on the diary card, including specified instructions as to which medicine and what doses to use for slight, moderate, and severe symptoms in the eyes, nose, and lungs.

The patients were also instructed to record the number of daily stools as well as diarrhea, abdominal pain, and abdominal swelling, graded from 0 to 3 in arbitrary units: 0 = none, 1 = slight, 2 = moderate, and 3 = severe symptoms. Other symptoms not normally experienced were also recorded. The recording of side effects started 2 weeks before capsule dosing and lasted as long as the patients were taking capsules. At each visit to the clinic, all diary cards were collected and checked, and new ones were delivered.

Occasional missing observations were substituted by weighed means, according to individual scores at specified pollen levels throughout the entire pollen season.⁸

In June 1983 and June 1984, just after the birch-pollen season, all patients were asked whether the allergic symptoms were better, unchanged, or worse compared with symptoms in birch seasons before entering the trial. In February 1984, one of us (E. T.) and the trial nurse tried to guess for each patient whether he/she was on active treatment or placebo treatment. This estimation was based on the SPT, CPT, and NPT results, symptom scores, and gastrointestinal side effects.

Skin prick test

Testing with birch was done in four replicates, two replicates on the volar side of each forearm. SPT with alder, elm, and hazel were done in duplicate. At each test session, six SPTs were aligned 3 cm apart in the following order, starting from the top of the forearm: histamine dihydrochloride, 10 mg/ml (positive control), albumin diluent (negative control), birch Pharmedgen, 100,000 BU/ml, 10,000 BU/ml, and 1000 BU/ml, and histamine dihydrochloride, 1 mg/ml (second positive control). The replicate on the same arm was done in the opposite order. The SPT with the other

three pollens consisted of histamine dihydrochloride, 10 mg/ml, Pharmedgen alder, 100,000 BU/ml, elm whole extract (Pharmacia), 1:45 (w/v), Pharmedgen hazel, 100,000 BU/ml, albumin diluent, and histamine dihydrochloride, 1 mg/ml. Wheal areas were recorded after 15 minutes and calculated as described earlier.¹¹

For each birch SPT session, a parallel line assay was done on the basis of median wheal areas for each of the four corresponding solutions.¹⁴ When individual birch SPT parallel line assays were compared, the amount of birch-allergen extract eliciting the same reaction as at the start of the trial was calculated.

All SPTs were performed by the same nurse who, in a preliminary trial¹³ (nurse I), had demonstrated a reproducibility in SPT within the recommended $\pm 20\%$ from the mean. The use of antihistamine and local steroids was avoided for at least 72 hours before SPT, inhaled corticosteroids for 48 hours, and bronchodilating medicine, both tablets and aerosol, for 6 hours.

Nasal and conjunctival provocation test

The NPT was carried out as described earlier¹⁵ with the dose increased stepwise by 0.5 log¹⁰. Pharmedgen birch, 1, 3.2, 10, etc., up to 320,000 BU/ml, was used. Each NPT was started with albumin diluent as negative control. The test solution 0.2 ml was atomized into the nose with a DeVilbiss (DeVilbiss Co., Somerset, Pa.) spray No. 15, three puffs into each nostril. Every 10 minutes, an increasing allergen concentration was administered until a positive reaction (or top concentration) expressed in biologic units and defined as the nose sensitivity to birch was reached. The reaction was defined as positive if two of the following three criteria were fulfilled within 10 minutes of provocation: more than five sneezes, >0.5 ml of secretion, and >20% decrease in nasal peak flow. Before NPT, all medication that could influence the result was withdrawn.

The CPT was performed as previously described.¹⁶ Each CPT was preceded by an inspection of the eye, and in the case of congestion or complaint of itching, CPT was not performed. If no such symptoms were present, one drop of the albumin diluent was instilled into the inferior conjunctival sack. If no reaction occurred, i.e., no congestion or itching, one drop of Pharmedgen birch dilution, 1 BU/ml, was instilled into the other eye after 10 minutes. The provocation doses were increased by half logarithmic steps in the alternate eye to positive reaction or top dose used for NPT. The criteria for positive CPT were congestion of the conjunctival mucosa and itching of the eye. All CPTs were performed by two persons only, one nurse and one of the authors (E. T.). Before CPT, all medication that could influence the result was withdrawn.

Birch pollen data

The symptom and medication scores were analyzed and compared with the birch-pollen counts registered in Copenhagen. The pollen trap and the method for analyzing pollen have been previously described.⁸ In order to analyze symptom and medication scores, the birch-pollen season was divided into three periods, each comprised of an equal num-

ber of days. Therefore, we obtained low, medium, and high pollen periods for each year. Because of very different cumulative pollen counts for these 2 years, the cutoff points for the periods differ (Table III).

Statistical methods

In order to test whether the two groups were comparable concerning age, sex, initial NPT, CPT, and SPT results, the Mann-Whitney test was used.

Since symptom, medication, and side effect scores were measured on ordinal scales, nonparametric methods were used for the statistical analysis with 95% confidence limits for the difference between the sum of medians in two groups.¹⁷ A comparison between the groups of logarithmically transformed daily symptom and medication scores has also been performed, as described by our group in a similar, previous study.⁸ Student's *t* test was used to analyze differences within and between the groups with respect to the CPT and NPT results. To normalize the distribution of results, the values were logged before analysis.

A parallel line assay was used to calculate the change in skin sensitivity to birch pollen during OIT.¹⁴ In regard to the other three SPT results, medians were calculated for each duplicate, and an analysis of variance was performed to test the differences between the groups.

An analysis of variance was carried out on the CPT and NPT results. To calculate the efficacy as assessed by patients and investigators, a chi-square test was performed. All data were calculated according to a scheduled plan before breaking the code, and no new methodology was applied later.

RESULTS

Symptom and medication score

Three patients failed to produce adequate symptom and medication scores in 1984 and were thus excluded from the analysis. This procedure did not introduce any bias, since it could be demonstrated that a substitution of the missing 1984 data by the 1983 data did not alter the conclusions. Missing observations in patients completing the study did not affect the results, since there was no significant difference between the two groups concerning the number of patients and the number and types of missing data substituted (all *p* values > 0.10). The two groups were comparable concerning both age and sex, as well as concerning the initial results of NPT, CPT, and SPT (*p* values > 0.50). Since no significant interaction between the treatment effect and the birch-pollen seasons of 1983 and 1984 could be demonstrated (e.g., the difference between the treatment groups was the same for both years), the overall statistical analysis was based on the sum of symptom/medication scores for both pollen seasons for each individual patient.

The individual medians of eye and nose symptom scores were calculated for 1983 and 1984, and the sum of these medians was used for comparison between groups. The difference between them (and 95%

TABLE IV. Difference between treatment medians of placebo and active group (95% confidence limits for difference)

	Symptom scores	
	Nose	Eye
Difference between medians		
Placebo-treated and actively treated group	19	29.2
95% Confidence limit	+48.2 to -6.0	+55 to +5.6
Significant difference between placebo-treated and actively treated group	NS	<i>p</i> < 0.05

NS = not significant. If 0 is within the limits, the H_0 hypothesis cannot be rejected.

confidence limits for medians) is presented in Table IV. Eye symptom scores were significantly lower in the actively treated group than in the placebo-treated group. Nose symptom scores differed in the same direction (but not significantly).

The conclusions obtained from logarithmically transformed scores were the same. When the two years are analyzed separately, the conclusions become weaker for statistical reasons, but the tendencies concerning the two treatments were the same for both years. Even dividing symptom scores according to the three pollen groups did not affect the conclusions presented (Table V).

Separate calculations of the sum (1983 plus 1984) of nose drops, eye drops, and prednisone tablets, according to the method mentioned above, demonstrated no significant differences between groups, but numerically, the placebo-treated group used most of all the kinds of backup antiallergic medicine. The overall daily medication scores demonstrated similar results. The figures for the three pollen count groups are presented separately for nose drops and eye drops (Table VI) in the same way as for symptom scores (Table V). The total medicine consumption in the placebo-treated group was significantly higher in 1984 than in 1983 (*p* < 0.01). A similar difference in the actively treated group could not be demonstrated (*p* > 0.10).

Seven patients in the actively treated group and eight patients in the placebo-treated group suffered from birch-pollen asthma. No difference at all was found between the groups concerning lung symptom scores.

TABLE V. Median values for sum of symptom score separately for birch season 1983 and 1984

Pollen level		Nose symptoms		Eye symptoms	
		Placebo	Active	Placebo	Active
1983	Low	7	6	6	4
	Medium	11	9	10	5
	High	13	9	11	8
1984	Low	6	3	8	1
	Medium	15	8	14	5
	High	18	10	19	8

TABLE VI. Median values for sum of nose and eye drops for the three pollen count groups for birth season 1983 and 1984

Pollen level		Nose medicine		Eye medicine	
		Placebo	Active	Placebo	Active
1983	Low	0	0	5	0
	Medium	4	0	8	2
	High	10	2	20	2
1984	Low	4	0	10	0
	Medium	12	0	16	0
	High	11	0	18	0

Skin prick test results

The changes in skin reactivity to birch-allergen preparation as measured by parallel line assay are presented in Fig. 1. During the study, no significant change was found in the placebo-treated group, whereas there was a highly significant decrease ($p < 0.001$) in the actively treated group. Regarding changes since the start of the trial, there was a significant difference between the two groups in January 1984 ($p < 0.01$) and in June 1984 ($p < 0.001$).

Changes in SPT regarding the other three tree pollens (wheal area evaluated in percent of the area elicited by 10 mg of histamine dihydrochloride) demonstrated no significant differences between groups at the beginning (all three tree pollens), and this was also the case for alder throughout the study. Hazel demonstrated a significant difference between the groups in January 1984 ($p < 0.03$) and elm in March 1983 ($p < 0.01$); however, no difference in skin sensitivity was found between the groups from January 1983 to January 1984 regarding alder, elm, and hazel.

Nasal and conjunctival provocation test results

In October 1983 and January 1984, the threshold dose of CPT in the actively treated group was signifi-

cantly increased compared with initial values (2.6 times [95% confidence limit 1.3 to 5.4] and 4.4 times [95% confidence limit 2.2 to 9.1], respectively). This was not observed in the placebo-treated group. Likewise, a comparison between the two groups concerning changes in eye sensitivity demonstrated significant difference, $p < 0.05$ and $p < 0.01$, respectively. Furthermore, from January 1983 to January 1984, the nasal tolerance in the actively treated group increased, although this was not statistically significant.

Birch-pollen count

The annual cumulative birch-pollen count has been measured for 8 years in Copenhagen. Data are presented in Fig. 2. In the first year of the study, 1983, the birch-pollen count was below the average, but the year 1984 produced the highest birch-pollen count ever measured. The daily pollen count for the birch season 1983 and 1984 is illustrated in Fig. 3. To avoid interference with symptoms induced by grass-pollen allergy, we only included symptom and medication scores from the beginning of the birch seasons (i.e., April 22 in 1983 and 1984) to the beginning of the grass-pollen seasons (i.e., May 24, 1983, and May 22, 1984, respectively). The different pollen-count levels of low, medium, and high pollen groups are presented in Table III.

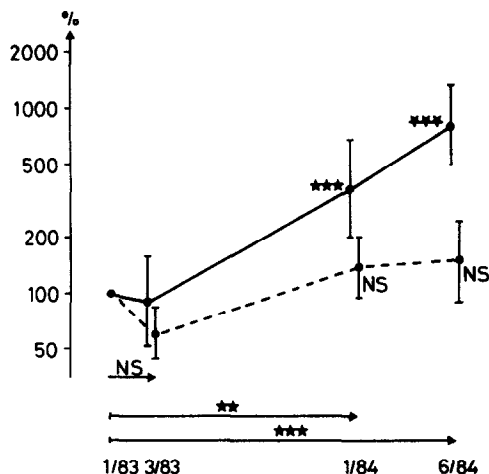


FIG. 1. Amount of birch-allergen preparation needed in SPT to elicit a skin reaction equal to the one produced before start of OIT. Solid line, actively treated group; dotted line, placebo-treated group. Vertical lines indicate 95% confidence interval. The difference in change from start within each group is indicated at the lines. Arrows indicate difference in change between groups from the start. NS, nonsignificant; ** $p < 0.01$; *** $p < 0.001$.

Assessment of efficacy by patients and investigators

When patients' assessments were compared to seasons before start of OIT, assessments revealed a significant difference in favor of the actively treated group (fewer symptoms), both in the 1983 and the 1984 season ($p < 0.05$).

At the end of the trial, the investigators were able to guess which group each patient belonged to ($p < 0.05$) (28 correct, five false placebo, and six false active).

Associated food allergy/intolerance

At the end of the study, 14 patients in the actively treated group were able to answer whether their food allergy/intolerance had changed. Seven patients were unchanged, and seven patients had improved. For the placebo-treated group, the figures were 14 and four, respectively, of the 18 responding. This difference between groups was not statistically significant.

Side effects

During the trial, no patients experienced capsule-induced anaphylactic reactions, asthma, or rhinitis, but one patient had an attack of urticaria during the dose-increase period at 70,000 BU daily. After withdrawing from the study for 1 week, the patient was able to continue the study without further attacks of urticaria. Gastrointestinal symptoms were the most frequent side effect. One patient suffering from irri-

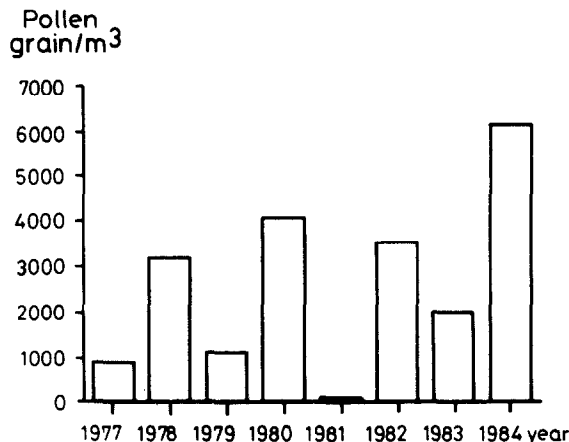


FIG. 2. Birch-pollen cumulative grains per cubic meter per year 1977 to 1984 measured at the Meteorological Institute, Copenhagen.

table colon for many years withdrew from the trial in June 1984 because of swelling of the stomach and fatigue 4 to 6 hours after intake of a capsule containing 600,000 BU. One patient in the placebo-treated group stopped treatment because of daily stomach pain and vertigo that disappeared when the patient stopped medication. During the dose-increase phase, eight patients in the actively treated group and two in the placebo-treated group stopped the capsule dosing for 1 week because of gastrointestinal side effects (abdominal swelling, pain, and/or diarrhea). They continued receiving a reduced dose before increasing the dose again. In the actively treated group, two patients experienced gastrointestinal symptoms at 70,000 BU daily, and six patients at 210,000 BU daily, but not at any other dose level. In the number of patients with gastrointestinal symptoms (abdominal swelling and/or pain, and/or diarrhea), a statistically significant difference between the two groups could be found receiving a daily dose of 210,000 BU per day. All patients succeeded in reaching a maintenance dose of 600,000 BU/day in 1983 and 1.2 million BU/day in 1984, and it was uncommon for patients to have gastrointestinal side effects after tolerating the maintenance dose for 2 weeks.

In vitro tests

The results of the immunologic tests in blood, sputum, and tears will be presented elsewhere. There were no significant changes in liver and kidney function tests or in hematologic and urine analyses during the study.

DISCUSSION

The present study is the first placebo-controlled study demonstrating a treatment effect of OIT in adult

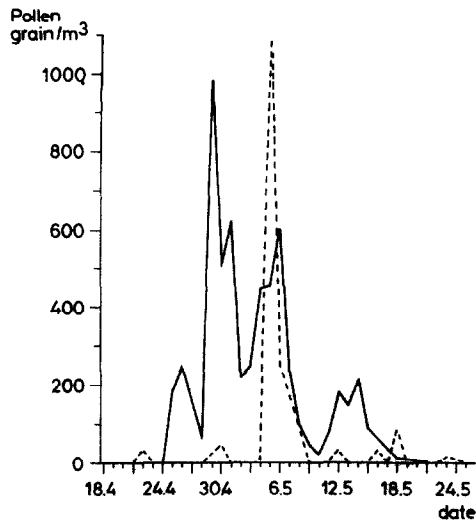


FIG. 3. Daily birch-pollen count in 1983 and 1984 measured at the top of the Meteorological Institute, Copenhagen. Solid line, 1984; dotted line, 1983.

patients with birch pollinosis. A corresponding effect has been demonstrated in a similar study in children.¹⁸

Symptom and medication scores

Such data are so-called soft data but, nevertheless, very important when a clinical treatment effect is to be proven. Based on SPT, NPT, and CPT data from the start of OIT, both groups were equally sensitive to birch pollen. Matching the two groups according to their symptom and medication scores in a pretreatment birch-pollen season would probably have been more nearly optimal.

Usually in hay fever trials, nose and eye symptom scores⁸ and even medication scores^{18, 19} are added to produce an overall symptom/medication score. Subsequently, the relationship between scores is unknown, which is unsatisfactory from a basic methodologic point of view. To overcome this problem, we therefore chose to keep the scores separate.

The confidence limits for the difference between treatment medians for nose symptoms presented in Table IV may be difficult to understand. The confidence limits could be interpreted in an informal way. In a hypothetical universal use of active treatment in patients with hay fever, it is unlikely on the average that such treatment would cause a deterioration in nose symptom scores >6 points during 64 days (two birch pollen seasons), and yet the treatment could conceivably cause an improvement in symptom scores, although the improvement would probably not be >48 points.

Since the cumulative pollen count in the first season was low and in the second season, extremely high, we were not surprised by the significant increase in

medication score from 1983 to 1984 observed in the placebo-treated group. A corresponding increase could not be demonstrated in the actively treated group that might indicate a treatment effect, since both eye and nose symptom scores were reduced from 1983 to 1984. Regarding the clinical results presented in Tables V and VI, it should be stressed that the improvement in the actively treated group compared to the placebo-treated group is clinically valid.

Skin prick test and conjunctival and nasal provocation tests

The fact that all SPTs were performed by the same test nurse, who in a previous study had demonstrated an excellent reproducibility,¹³ is highly beneficial from a methodologic point of view. To our knowledge, no convincing study exists concerning the reproducibility of nasal allergen challenge. This might be the reason why the increase in NPT in this study was only numerically contrary to the significant increase in CPT (actively treated group). Möller et al.¹⁶ have demonstrated a high reproducibility of allergen CPT.

Assessment of efficacy

After both birch-pollen seasons, the patients were able to distinguish between treatment and placebo groups within 5% significance limits. The initial dose-increase regimen was modified in eight actively treated patients and in two placebo-treated patients. Gastrointestinal side effects occurred significantly more often in the actively treated group but only on one-dose step, e.g., 210,000 BU/day. The fact that the patients were able to distinguish between treated groups is therefore most likely based on a treatment effect and not on side effects.

Food-associated allergy/intolerance

Whether OIT can diminish or even cure the commonly associated food intolerance in birch pollinosis is unclear. We could not demonstrate such an effect during active treatment, probably because the study was not designed to elucidate this problem. If this had been the study design, patients would have been matched according to food allergy/intolerance, and oral provocation test with the food item in question, e.g., such as hazel nut, before and after the study, would have been performed.

Side effects

Various side effects caused by OIT (aqueous allergen extracts and pollen powder) have been reported.^{3, 20, 21} Stomach pain and mild diarrhea are by far the most common. Conjunctivitis and/or rhinitis, asthma attacks, generalized urticaria, and vomiting, however, are seldom observed. Contrary to most stud-

ies, we used enteric-coated tablets, such as in a few other studies.^{8, 18, 21-24} We found one case of extraintestinal side effect (mild urticaria). Asthma as well as hay fever have been reported in studies with enteric-coated tablets.²¹

Likewise, in a similar study in children,¹⁸ only mild gastrointestinal side effects were observed, which might be caused by the more slow and moderate dose-increase schedule.

Furthermore, some cases of anaphylaxis in pollen-sensitive patients have been reported in connection with ingestion of health food known as "bee pollen" containing dandelion pollen that belongs to the Compositae family.²⁵ To start OIT with high allergen doses should therefore be avoided.

It appears rather peculiar that OIT with enterosoluble grass-pollen capsules has not demonstrated any clinical or serologic changes. This might be caused by rapid disintegration of the allergenic sites in grass pollen when it is dissolved in enteric fluid. Preliminary studies indicate that the allergenic components in birch pollen are more stable in intestinal fluid than those in grass pollen. Before starting placebo-controlled OIT trials with other allergens, it therefore appears wise to test the stability of each new allergen preparation in the intestinal fluid. If the disintegration is fast, certain procedures should be carried out to protect the allergenic sites against destruction.

CONCLUSION

This study demonstrates that OIT in birch pollinosis is clinically effective. The conclusion is supported by a significant decrease in eye symptom scores and conjunctival birch-pollen sensitivity (i.e., increase in CPT threshold dose), as well as reduced skin sensitivity, and a numerical, although it is not significant, decrease in nasal symptom score, nasal sensitivity (i.e., increase in NPT threshold dose), and antiallergic medication. The treatment is safe, and only a few mild side effects were observed.

The skillful assistance of Mrs. Birgitte Skovsted who performed most of the allergologic tests is gratefully acknowledged.

REFERENCES

- Urbanek R, Kuhn W, Binder U. Untersuchungen zur Wirksamkeit oraler und parenteraler Hyposensibilisierung mit Pollen-Extrakten. *Dtsch Med Wochenschr* 1938;38:1433.
- Rebien W, Puttonen E, Maasch HJ, Stix E, Wahn U. Clinical and immunological response to oral and subcutaneous immunotherapy with grass pollen extracts. *Eur J Pediatr* 1982;138:341.
- Wortmann F. Oral hyposensitization of children with pollinosis or house-dust asthma. *Allergol Immunopathol (Madr)* 1977;15:15.
- Wahn U, Maier A, Geiger H. Orale hyposensibilisierung bei pollenallergien im kindesalter. *Monatsschr Kinderheilkd* 1976;124:245.
- Curtis H. The immunizing cure of hay fever. *Med News* 1900;77:16.
- Stemann EA, Wegner F, Schachoff R, Reinhardt D. Orale Hyposensibilisierung bei Kindern. *Prax Klin Pneumol* 1979;33:302.
- Wortmann F. Orale desensibilisierung. *Allergologie* 1979;5:243.
- Taudorf E, Laursen LC, Djurup R, Kappelgaard E, Pedersen CT, Søborg M, Wilkinson P, Weeke B. Oral administration of grass pollen to hay fever patients. *Allergy* 1985;40:321.
- Urbanek R, Gehl R. Wirksamkeit oraler hyposensibilisierung bei hausstaubmilbenallergie. *Monatsschr Kinderheilkd* 1982;130:150.
- Feinberg SM, Foran FL, Lichtenstein MR, Padnos E. Rapaport BZ, Sheldon J, Zeller M. Oral pollen therapy in ragweed pollinosis. *JAMA* 1940;115:23.
- Cooper PJ, Darbyshire J, Nunn AJ, Warner JO. A controlled trial of oral hyposensitization in pollen asthma and rhinitis in children. *Clin Allergy* 1984;14:541.
- Dreborg S. Standardization of allergen preparations by means of skin prick testing. In: Dieges PH, de Monchy JGR, eds. Skin test and RAST procedures in the standardization of allergenic extracts [in press]. Amsterdam: Excerpta Medica.
- Taudorf E, Malling HJ, Laursen LC, Lanner Å, Weeke B. Reproducibility of histamine skin prick test. *Allergy* 1985;40:344.
- Finney DJ. Statistical method in biological assay. United Kingdom, Charles Griffin & Co Ltd, 3rd ed. 1978.
- Østerballe O. Immunotherapy in hay fever with two major allergens 19, 25 and partly purified extract of timothy grass pollen. *Allergy* 1980;35:473.
- Möller C, Björkstén B, Nilsson G, Dreborg S. The precision of the conjunctival provocation test. *Allergy* 1984;39:37.
- Hollander M, Wolfe DA. Nonparametric statistical methods. New York: John Wiley & Sons, 1973:78.
- Möller C, Dreborg S, Lanner Å, Björkstén B. Oral immunotherapy of children with rhinoconjunctivitis due to birch pollen allergy: a double-blind study. *Allergy* 1986;41:271.
- Østerballe O. Immunotherapy with grass pollen major allergens. *Allergy* 1982;37:379.
- Black JH. The oral administration of ragweed pollen. *Allergy* 1939;10:156.
- Thiberge NF. The use of enteric-coated pills in allergic states. *New Orleans M & S J* 1942;94:390.
- Touart MD. Hay fever: desensitization by ingestion of pollen protein. *NY Med J* 1922;116:199.
- Björkstén B, Möller C, Broberger U, Ahlstedt S, Dreborg S, Johansson SGO, Juto P, Lanner Å. Clinical and immunological effects of oral immunotherapy with a standardized birch pollen extract. *Allergy* 1986;41:290.
- Björkstén B, Croner S, Dreborg S, Lanner Å. A double-blind study of oral immunotherapy (OIT) in children allergic to birch pollen using high doses of allergen [Abstract]. *J ALLERGY CLIN IMMUNOL* 1986;77:214.
- Cohen SH, Yunginger JW, Rosenberg N, Fink JN. Acute allergic reaction after composite pollen ingestion. *J ALLERGY CLIN IMMUNOL* 1979;64:270.