

A Double-Blind, Multicenter Immunotherapy Trial in Children, Using a Purified and Standardized *Cladosporium herbarum* Preparation

I. Clinical Results

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A double-blind histamine placebo controlled immunotherapy trial was performed to investigate the clinical effect of a purified and standardized *Cladosporium herbarum* allergen preparation. Thirty children with a clinical history suggesting mould-induced asthma and/or rhinoconjunctivitis were included. The diagnosis was confirmed by positive skin prick test and Phadebas RAST[®] as well as positive bronchial and/or conjunctival provocation test to *Cladosporium herbarum*. Immunotherapy was given for 10 months in a double-blind manner to randomized groups with either Pharmalgen[®]/*Cladosporium herbarum* preparation or histamine placebo. Allergic side effects to injections were common, especially during the peak of the mould season (July-September in Scandinavia). In the active group, 13/16 patients experienced general reactions during the first 10 months of treatment. After 6 months of treatment, eye, nose and bronchial symptom scores and peak expiratory flow rates were similar for the groups, maybe because most of the children were also sensitive to many other allergens, including *Alternaria alternata*. However, medication scores were significantly lower in the treated group ($P < 0.01$). Bronchial ($P < 0.01$) and conjunctival sensitivity ($P = 0.01$) were significantly reduced in the *Cladosporium*-treated group but not in the placebo group after 10 months of treatment. This is the first double-blind clinical trial showing the clinical efficacy of immunotherapy in children with mould-induced asthma.

Key words: *Cladosporium herbarum*; mould allergy; purified allergen preparation; bronchial provocation test; conjunctival provocation test; immunotherapy; medication score; patient score; peak expiratory flow; skin prick test; spore count.

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CLINICAL ASPECTS

Knowledge about mould allergens and mould allergy has been scarce, the quality of mould allergen extracts, has, up to now, been low and no immunotherapy trial using mould extracts has shown that they are efficacious. Therefore, immunotherapy with mould extracts has not been widely accepted. As it is now shown that it is possible to increase the tolerance to mould extracts by immunotherapy with a purified, potent and well-characterized *Cladosporium* preparation, this will increase the justifiable use of immunotherapy in the often multi-allergic patients with mould allergy, and represents a step forward in the treatment of patients with mould allergy.

Mould spores and mycelia are abundant in our environment. Much attention has been paid to the possible significance of mould allergens in allergic asthma (16). It has been clearly shown that the previously available mould extracts did not have the capacity to diagnose all patients with mould allergy in skin prick testing (4, 11).

Immunotherapy with mould extracts has not been shown effective in double-blind studies (16), but Goldstein & Chai (9) have reported a reduced specific bronchial sensitivity in a few patients treated with *Cladosporium* and/or *Alternaria* extracts.

The most prevalent mould in Scandinavia is *Cladosporium herbarum*, which has an extremely complex allergenic composition and is rapidly degraded in aqueous solution (3).

When a highly purified, biologically standardized and potent *Cladosporium herbarum* preparation with known antigenic and allergenic composition (3) was made available to us, a study was designed to evaluate the efficacy of immunotherapy (hyposensitization) with this preparation in children with mould-induced asthma.

MATERIAL AND METHODS

Patients

Thirty children, 14 boys and 16 girls with a mean age of 11 years (range 5–17) participated in the study. Ten children were from Linköping and 13 from Uppsala, Sweden, and seven were from Turku, Finland. All had a clinical history indicating possible mould allergy. Primary screening was performed as described earlier (11).

Inclusion criteria were a typical history with start or worsening of asthma during the *Cladosporium* season (June–October), a positive skin prick test – 2+ or more (2) with a *Cladosporium herbarum* preparation (1,000 BU/ml) or 3+ or more with the same preparation (5,000 BU/ml) (Nyegaard & Co., Oslo, Norway), and/or *Cladosporium herbarum* specific serum IgE of class 1 or higher (Phadebas RAST®, Pharmacia AB, Uppsala, Sweden).

All patients had such severe symptoms that

they wished to participate. The families were given verbal and written information and the parents gave their consent. The study was approved by the Ethics Committees at all three hospitals.

Excluded from the trial were patients on immunotherapy with mould extract for the last 2 years, with chronic cardiovascular, cardiopulmonary or immunological diseases, with severe generalized eczema, or on continuous systemic corticosteroids in the month prior to the onset of the study.

All patients complied with symptom scoring, blood sampling and skin prick testing according to the protocol. Three patients were excluded from the calculations of conjunctival provocation test results due to negative pre-treatment tests. Bronchial challenge was not performed in two patients in the actively treated group due to continuous symptoms and in two patients, one from each group, due to lack of compliance at follow-up. These patients were excluded from the bronchial provocation calculations. Twenty-four of the 30 patients were also skin prick test positive to *Alternaria alternata*. Twenty patients had specific IgE antibodies (Phadebas RAST class ≥ 1) to dog, 24 to cat, 18 to horse, 19 to mugwort pollen (*Artemisia vulgaris*), 22 to timothy pollen (*Phleum pratense*) and 22 to birch pollen (*Betula verrucosa*). Only one patient did not react to any of the six tested allergens.

Materials

A purified and standardized *Cladosporium herbarum* allergen preparation (Pharmalgen®) was obtained from Nyegaard & Co., Oslo, Norway and Pharmacia AB, Uppsala, Sweden. *Cladosporium herbarum* was grown on synthetic medium. To minimize the variation in allergenic composition between batches (17), consistent growth conditions were used and equal amounts of material (mycelia and spores) from 10 strains were mixed. Two mixed batches were used as raw material. The extraction and purification were essentially performed as previously described (7). The product was freeze-dried, reconstituted and diluted to four concentrations with predetermined biological activity. The

final product was delivered freeze-dried in the concentration of 100, 1,000, 10,000 and 100,000 Biological Units (BU)/ml. The same production batch was used throughout the study. To reconstitute the preparations, Albumin diluent (0.03 % human albumin in saline) was used for diagnosis and the initial treatment. Depot diluent (0.20 % $\text{Al}(\text{OH})_3$ and 0.4 % phenol (in saline)) was used during the maintenance treatment. Freeze-dried, caramelized histamine HCl, 0.01, 0.03, 0.1 mg/ml reconstituted as above, was used as placebo.

Medication prior to tests

To avoid its influence on test results, medication was stopped prior to SPT, CPT, and BPT at different times depending on the type of medication. The shortest intervals are given in Table 1.

Skin prick test (SPT). The freeze-dried allergen preparation was reconstituted and diluted with Albumin diluent on the day of the test. Duplicate SPT according to the method of Pepys (14) were performed with 1,000, 10,000 and 100,000 BU/ml as well as with histamine HCl, 1 mg/ml.

The skin reaction was recorded after 15 min. The wheal contour was encircled with a fine filter tip pen and transferred to a patient record sheet by means of transparent tape. The area of each wheal was calculated with a digitizer. The change in sensitivity of each patient during therapy was calculated at 100,000 BU/ml by using the logarithmic difference in wheal area as a percentage of the histamine wheal.

Conjunctival provocation test (CPT) was performed essentially according to Möller et al. (10) using half logarithmic increments with 10 min intervals (10, 32, 100, ... 100,000 BU/ml).

Bronchial provocation test (BPT) was essentially performed according to Aas (1). Peak expiratory flow (PEF) rate was used as an objective parameter. The patients were trained to obtain reproducible PEF results. The maximum of the three PEFs was used. Registration of PEF and auscultation were performed prior to and 15 min

after each challenge. Initially, patients were challenged with diluent followed by 10-fold increasing concentrations of the *Cladosporium herbarum* preparations (1, 10, 100, 1,000, 10,000, and 100,000 BU/ml), reconstituted on the day of the test, at 15-min intervals. A standard Pari Inhaler-Boy nebulizer with a mouthpiece was used before and after treatment. A positive reaction was registered if the patient was showing typical asthma and a reduced PEF value of 15 % or more. Full medication was given as soon as a positive reaction occurred. The patient was observed for 30 min after a positive test.

Spore counts

Burkard volumetric spore traps were placed at roof level (10–15 m high) on a factory building in Uppsala, on the hospital in Linköping and on the University building in Turku. Daily spore counts were obtained from June until late October. The spores were sampled at an air flow of about 10 l/min on cellophane tapes coated with a thin film of vaseline-paraffin wax in toluene. The exposed tapes were cut into lengths of 48 mm, each corresponding to 24 h of sampling. Each piece of tape was mounted on a microscope slide with gelvatol or glycerine jelly. The slides were analysed under a microscope in $\times 625$ magnification. On each slide 48 squares, with an area of about $48,000 \mu\text{m}^2$, were counted, giving a factor 20 for conversion of number of spores counted to number of spores per m^3 . Four squares were analysed along each of the 12 transverse lines, evenly

Table 1

Shortest intervals (hours) between last medication and tests

Medication	SPT	CPT	BPT
Antihistamines	72	72	72
β_2 -stimulators			
oral	12	18	18
inhaled	–	18	18
Disodium cromoglycate	–	24	24
Theophylline	18	18	18
Beclomethasone dose aerosol	1 week	1 week	1 week

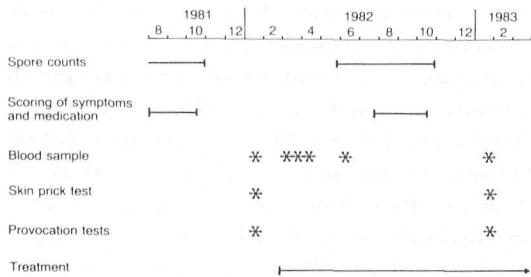


Fig. 1. Design of the study. Patient scoring and diagnostic procedures.

spaced 4 mm apart, corresponding to every 2 h of sampling.

Symptom score

All patients registered nasal symptoms (sneezing, rhinorrhea and occlusion, separately), ocular symptoms (redness, itching and swelling, separately) and bronchial symptoms graded 0-3 (none, slight, moderate, and severe). Symptoms during the day and night were recorded separately and added before statistical evaluation.

Medication scores

In principle, routine daily treatment was kept to a minimum and the drugs were introduced in one and the same order. The basic drug in the treatment of asthma was terbutaline or salbutamol tablets (Bricanyl®, Ventoline®, Salbutivent®). If this treatment was not enough, theophylline (Teovent®) and, as a third possibility, disodium cromoglycate (Lomudal®) was allowed. If the patient had severe complaints, beclomethasone dipropionate (Becotide®) 100 µg three times a day was given. An inhaled β₂-stimulator (Ventoline) was allowed when required.

Basic treatment for nasal symptoms was dexchlorpheniramine maleate (Polaramin®, Sensidyne®) or clemastine (Tavegil®). If necessary, beclomethasone dipropionate (Becotide nasal®) was added at the lowest possible dose. Alpha-adrenergic nose drops (Nezeril®, Nasoline®) and alpha-adrenergic and antihistamine eye drops (Antasten-Privin®, Oftan-Starine®) were allowed when required. The total number

per 24 h of tablets, capsules, puffs and drops made up the daily score.

Lung function assessment during season

PEF was registered every morning and afternoon. The highest value of three registrations was noted.

Study design

All patients recorded symptom and medication scores and PEF for a 10-week period at the peak of the *Cladosporium* season (August to beginning of October in Scandinavia), before treatment (1981) and after 5-7 months of treatment (1982). Diagnostic procedures were performed according to Fig. 1.

Immunotherapy

The patients were allocated into blocks of four according to their bronchial sensitivity, and

Table 2
Dose schedule for immunotherapy with Pharmalgen®/*Cladosporium herbarum* and a placebo preparation

Week No.	Dose No.	Volume No.	Pharmalgen/ <i>Cladosporium herbarum</i>		
			Conc., BU/ml	Dose, BU	Cumulative dose, BU
1	1	0.1	100	10	10
	2	0.2	100	20	30
	3	0.5	100	50	80
3	4	0.1	1,000	100	180
	5	0.2	1,000	200	380
	6	0.5	1,000	500	880
5	7	0.1	10,000	1,000	1,880
	8	0.2	10,000	2,000	3,880
	9	0.5	10,000	5,000	8,880
7	10	0.1	100,000	10,000	18,880
	11	0.1	100,000	10,000	28,880
	12	0.2	100,000	20,000	48,880
	13	0.2	100,000	20,000	68,880
11	14	0.3	100,000	30,000	98,880
	15	0.3	100,000	30,000	128,880
13	16	0.4	100,000	40,000	168,880
	17	0.4	100,000	40,000	208,880
15	18	0.5	100,000	50,000	258,880
	19	0.5	100,000	50,000	308,880
18	20	1.0	100,000	100,000	408,880
22	21	1.0	100,000	100,000	508,880
etc. every 4th week.					

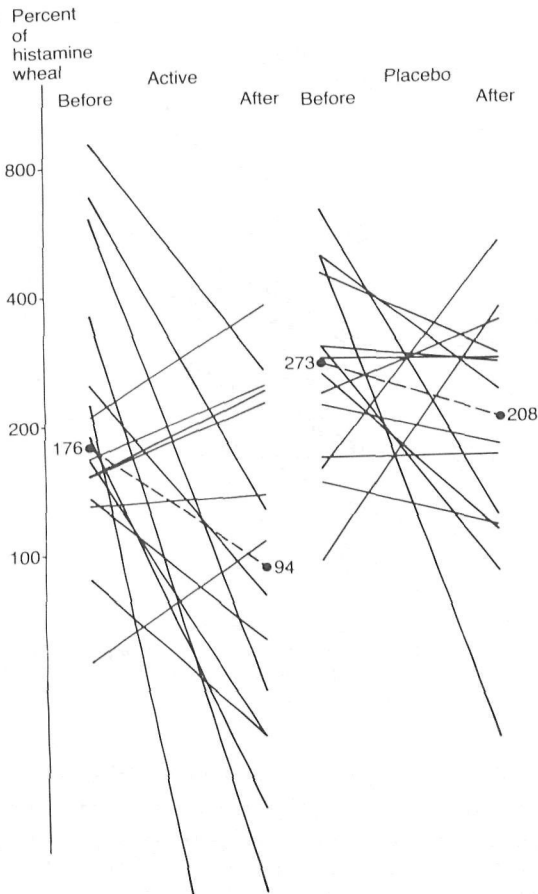


Fig. 2a. Individual wheal mean size of *Cladosporium*, 100,000 BU/ml in percent of the histamine wheal (= relative skin sensitivity (—) and the median of the whole group (-----) before and after 10 months of immunotherapy.

randomized to treatment with the standardized *Cladosporium herbarum* preparation (16 patients) or histamine placebo (14 patients). Treatment was given with the freeze-dried material, reconstituted in Albumin diluent according to a

Table 3

Lowest dose (BU) causing general reactions

Dose BU	Children <i>n</i>
1,000	2
1,001-3,000	2
3,001-10,000	8
10,001-30,000	1
30,001-100,000	0
No reaction	3

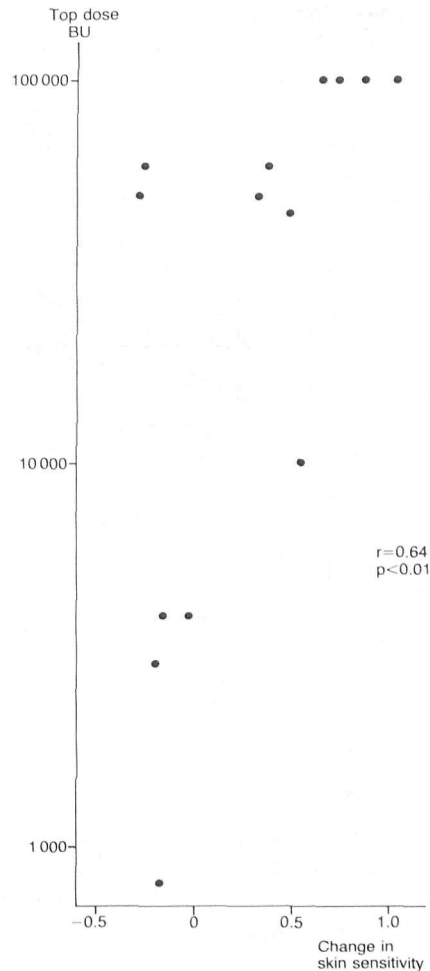


Fig. 2b. Change in relative skin sensitivity (10-log difference of wheal area in percent of the histamine wheal after 10 months of immunotherapy) in relation to the maximum dose.

“clustered” regimen (Table 2) and comprised three injections with 30-min intervals at each visit until a large local immediate reaction (> 5 cm swelling) or systemic reaction occurred. In the event of an immediate local reaction > 5 cm or a late local reaction > 10 cm in diameter, the same dose was repeated. With a general reaction the dose was reduced to 1/10th of that inducing the reaction. The dose was then increased according to the dose schedule. When 100,000 BU was reached, incremental doses of the material, reconstituted in Depot diluent, were given once a week until the highest tolerated dose was reached.

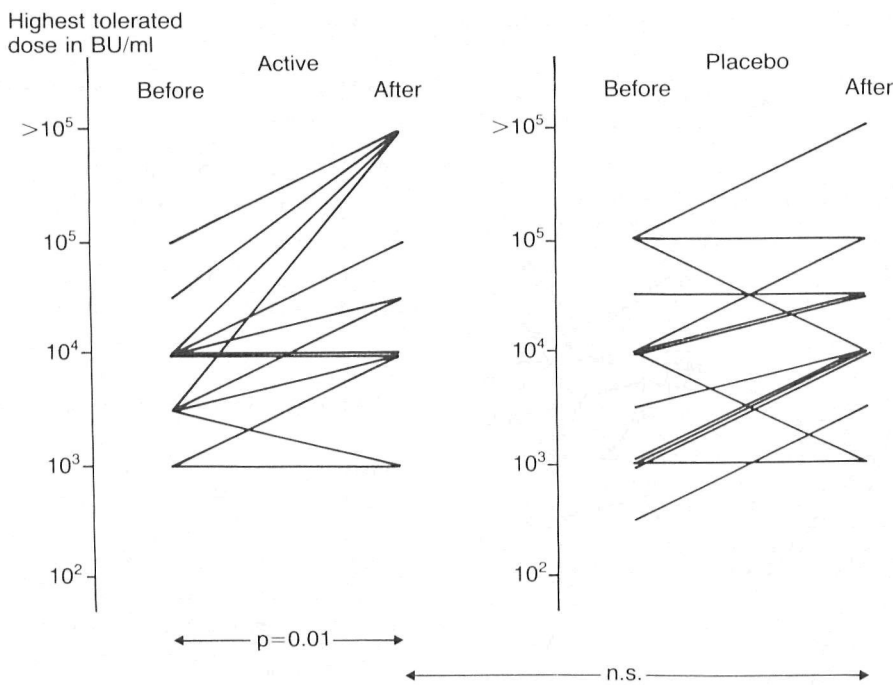


Fig. 3. Conjunctival threshold concentration before and after 10 months of immunotherapy.

Statistical calculations

For the statistical calculations Student's t-test was used for evaluation of changes within groups and Wilcoxon rank sum test for comparison between groups.

RESULTS

Of the 16 children treated with the *Cladosporium* preparation, five reached 100,000 BU, six patients between 30,000 and 60,000 BU and five patients less than 10,000 BU per injection day.

All patients receiving histamine placebo reached the highest maintenance dose without difficulty. Only minor local reactions were noted.

The lowest dose of the *Cladosporium herbarum* preparation causing general reactions differed considerably between patients (Table 3). All of them got asthma and three patients had urticaria as well. In total, 45 general reactions and four large local reactions (> 10 cm in diameter) occurred during the first 10 months of treatment (Table 4).

Skin sensitivity decreased in 10/16 actively treated patients (62 %) during the treatment period, whereas the sensitivity decreased in 6/14 (43 %) in the placebo group (Fig. 2a). However, the difference between the groups was not significant. The correlation between the top dose given and the change in skin sensitivity was good, $r = 0.64$, $P < 0.01$ (Fig. 2b).

The groups did not differ in conjunctival sensitivity before or after treatment (Fig. 3). However, tolerance increased significantly in the patients treated with the active material (P

Table 4

The number of general and large local reactions during the first 10 months of treatment

Type of reaction	Number				Patients %
	Total	Per patient	Per 100 injections	Per 100 visits	
General	45	2.9	10.2	18.2	81
Local > 10 cm diameter	4	0.25	0.9	1.6	25

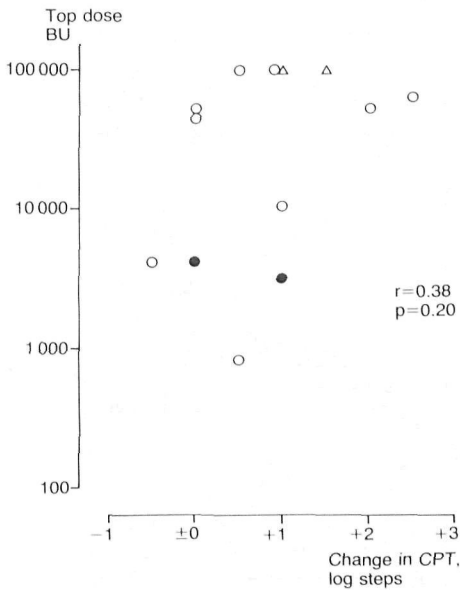


Fig. 4. Change in conjunctival sensitivity related to the maximum dose in BU. Conjunctival threshold concentration before treatment 1,000 BU/ml ●; 3,200–10,000 BU/ml ○; 32,000–100,000 BU/ml △.

= 0.01), but was unchanged in the placebo-treated group.

The correlation between the top dose given and the change of sensitivity in CPT was poor ($r = 0.38$, $P = 0.20$) (Fig. 4). The two most sensitive patients (●) reached lower concentrations than the two least sensitive (△) (Fig. 4).

Bronchial sensitivity did not differ between the groups before treatment. Patients treated with the active material, but not those with placebo, showed significantly improved bronchial tolerance ($P < 0.01$) after treatment, and their tolerance became significantly higher than that of the placebo-treated group ($P < 0.05$) (Fig. 5).

The correlation between the top dose given and the change of sensitivity in bronchial provocation test was poor ($r = 0.27$, $P < 0.36$).

No correlation was found between bronchial sensitivity before treatment and the change in bronchial sensitivity during 10 months of treatment ($P < 0.05$).

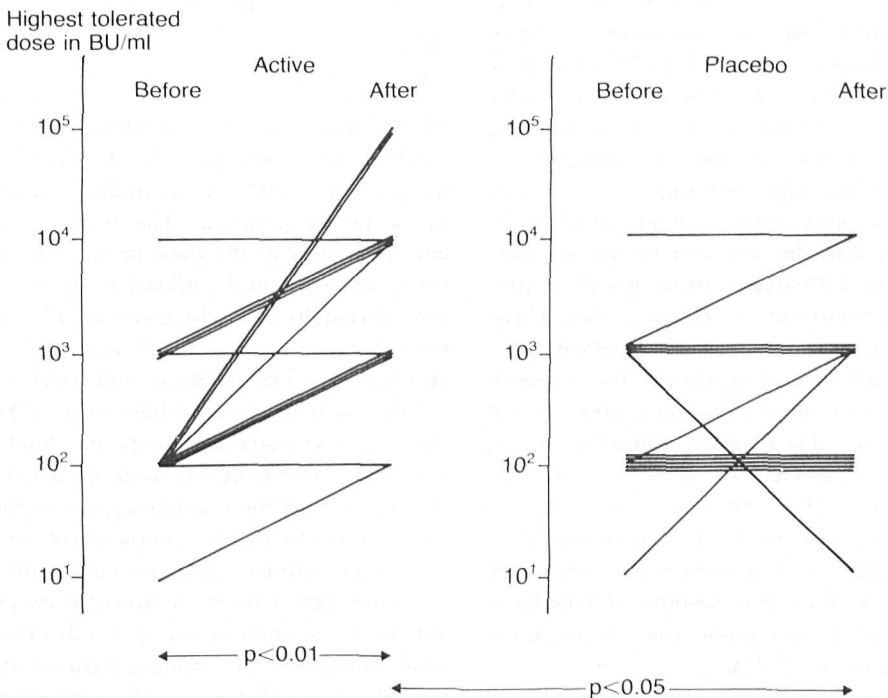


Fig. 5. Bronchial threshold concentration (BU/ml) before and after 10 months of immunotherapy in the two groups.

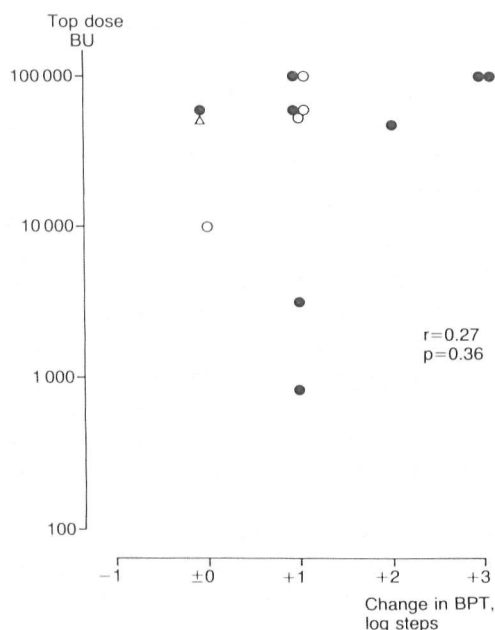


Fig. 6. Change in bronchial sensitivity related to the maximum dose in BU. Bronchial threshold concentration before treatment 10–100 BU/ml ●; 1,000 BU/ml ○; 10,000 BU/ml △.

The number of spores was calculated in all three locations as the means of spore counts/ m^3 and day during each week (Fig. 7). The spore counts in Linköping were lower than in Turku and Uppsala. In both years the peaks occurred between the end of July and the beginning of September at all three locations.

The two groups did not differ significantly regarding total medication and symptom scores during the total 10-week scoring period at pre-treatment (1981) or at evaluation (1982). However, when the 2 weeks with the highest spore counts in each year were chosen for comparison, the medication scores in the placebo group were higher in 1982 than in 1981 while in the actively treated group they were lower in 1982 than in 1981. The difference between the groups in 1982 was statistically significant ($P < 0.01$) (Fig. 8). The symptom scores were only slightly lower after 5–7 months of treatment compared with the corresponding 2-week period of the previous year (Fig. 8).

After 5–7 months of treatment, the PEF had become slightly higher in the actively treated

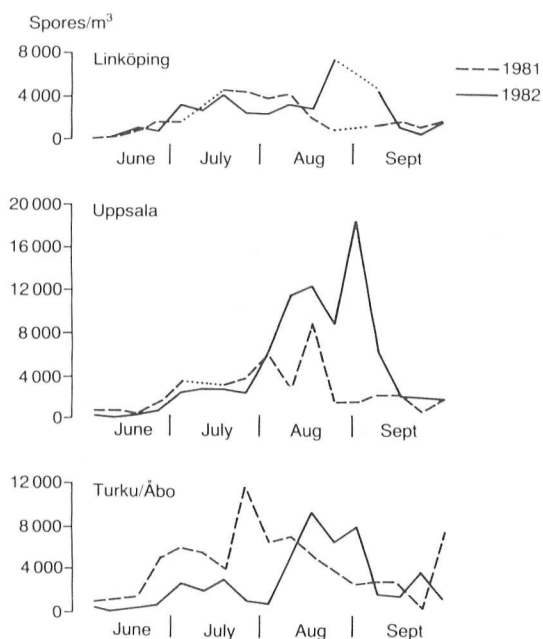


Fig. 7. Mean daily number of *Cladosporium* spores/ m^3 during each week 1981 ---- and 1982 — in the three centers.

group and slightly lower in the placebo-treated group but there was no significant difference between the groups (Fig. 8).

DISCUSSION

All children receiving the placebo preparation reached the maximum dose of “100,000 BU”, in contrast to only 5/16 children treated with the active preparation. The reason was probably that most of the patients were sensitive to many allergens and suffered from severe asthma. Although many allergens could be avoided, it was impossible to eliminate infections, pollens and moulds. The children with asthma due to animal allergen were probably also exposed to these in small amounts, e.g. at school. Thus, they showed more or less continuous symptoms, at least during the snow-free part of the year. The rather frequent general reactions, especially with asthma, probably reflect our aim to reach as high a maintenance dose as possible. When an allergen is injected subcutaneously, small amounts are rapidly released into the circulation and distributed throughout the body (6). Small amounts of allergen reach the lungs.

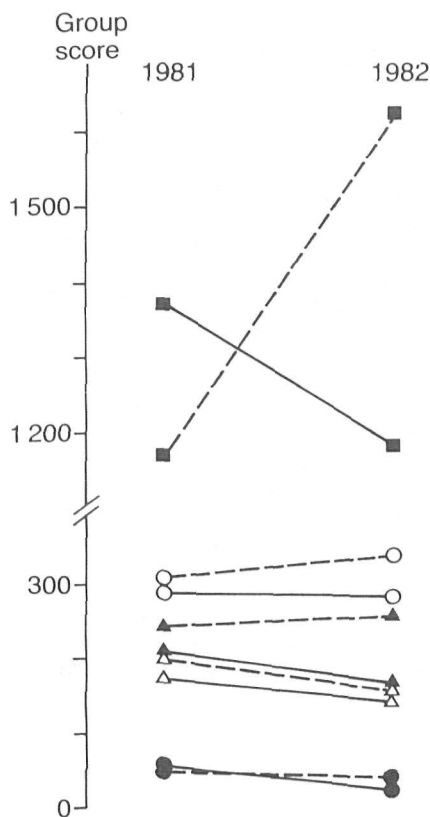


Fig. 8. Median values in the placebo group ---- and the *Cladosporium* group — of total medication scores ■, mean peak expiratory flow ○, bronchial ▲, nasal △, and ocular ● symptom scores during the 2 weeks with highest spore counts in 1981 and 1982.

As discussed by Cockcroft (5) and Platts-Mills (15) the intermittent exposure to allergens and irritants causes continuous hyperreactivity and a state of ongoing allergic inflammation in the bronchi. This is probably the reason for the increased number of general reactions, with asthma, that occur especially during the mould season in patients on immunotherapy.

The bronchial challenge, showing significant improvement in actively treated children, was performed in January/February when the mould spore count is negligible in Scandinavia. Only a few patients, mainly those with complicating animal allergy, showed symptoms during this period. Thus, most patients did not suffer from ongoing allergic inflammation at the time of the pre- and post-treatment challenges, and means that most of them were in the same

situation as pollen-sensitive patients challenged outside the pollen season. This is in contrast to mite-sensitive patients treated with immunotherapy who have no symptom-free periods during which challenge tests can be performed. This probably accounts for the less pronounced effects, as measured by bronchial provocation, found by Formgren et al. (8). It is not generally accepted that skin sensitivity, as measured by SPT, decreases during the treatment period. However, recent investigations utilizing standardized and freeze-dried materials, a prerequisite for such investigations, have shown a decreased skin sensitivity during immunotherapy (8, 10, 12).

Also conjunctival sensitivity decreased in the actively treated group, but no significant difference between the groups was found.

Although the objective challenge tests and skin tests showed definite improvement, the different parameters registered during the seasons were less conclusive. As most of the patients suffered from asthma that could be easily provoked by several different allergens, by infections, exercise and other non-immune mechanisms, it is not surprising that treatment with one mould allergen failed to give significant improvement during the entire mould season. Any improvement due to treatment would probably be better seen during a shorter period with high mould spore counts. A comparison of data obtained during the 2 weeks of the year when spore counts are highest showed no significant improvement in PEF rate or symptom scores between 1982 and 1981. However, the medication scores decreased significantly in the actively treated group compared to the placebo group, in spite of higher spore counts during the 2-week period in 1982.

The most probable explanation for the decrease in medication scores but not symptom scores is that patients suffering from continuous asthma tolerate some of their symptoms. When their asthma improves due to immunotherapy, they prefer to decrease medication rather than continue the same medication but with fewer symptoms. This was also in agreement with the instructions given to the patient.

Although the improvement obtained may not

seem impressive, these patients were multi-sensitive, and it is interesting to note that their clinical status was influenced by a few months' treatment with the *Cladosporium* preparation. This clearly shows the clinical importance of *Cladosporium* allergy in patients with severe asthma and mould allergy. The ideal trial for evaluation of immunotherapy in *Cladosporium* allergy would include patients sensitive only to *Cladosporium herbarum*, but such patients are rare.

In conclusion, this is the first double-blind histamine placebo controlled trial showing the clinical efficacy of immunotherapy using a mould preparation in children with asthma.

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