

Diagnosis and Immunotherapy of Mould Allergy

V. Clinical Efficacy and Side Effects of Immunotherapy with *Cladosporium herbarum*

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A placebo-controlled, double-blind study of immunotherapy with the mould species *Cladosporium* was performed in 22 adult asthmatics. The diagnosis of *Cladosporium* allergy was based on a combination of bronchial provocation test and daily symptom score in the *Cladosporium* season. An aqueous preparation of a potent, biologically standardized and purified extract was used in a clustered dose-increase regimen. The clinical efficacy was evaluated by a combination of symptoms (asthma score + peak flow) and consumption of antiasthmatic medication. The mean changes in symptoms and medication consumption over a 10-week registration period (peak *Cladosporium* season) in 1982 after 5-7 months of immunotherapy were compared with the corresponding 1981 pretreatment 10-week period. A significant ($P = 0.03$) difference in terms of "improved", "unchanged" and "deteriorated" patients in favour of *Cladosporium* treatment was found. Approximately 80% in the *Cladosporium* group showed improved/unchanged symptoms contrary to 30% of the placebo treated. Side effects were observed frequently but only in the *Cladosporium*-treated. About 70% experienced a large local reaction and 100% had episodes of asthma during dose-increase phase. Only a few severe systemic reactions occurred. Based on the clinical efficacy of the treatment we consider immunotherapy with *Cladosporium* feasible for highly specialized clinics.

Key words: asthma; clinical efficacy; immunotherapy; mould allergy; side effects

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The role of pollen and mould spore exposure in inducing respiratory allergy symptoms has been known since the time of Blackley (7). The correlation between mould spores and asthma was first pointed out by van Leeuwen (25) and has recently been confirmed (17).

The clinical efficacy of immunotherapy as the foundation of specific allergic treatment is well documented (20), and has been demonstrated primarily with pollen and house dust mite, but very few with animal dander (19, 20). Hay fever is the most common allergic disease studied and data concerning the treatment of asthma are scant (14, 20).

Studies on immunotherapy employing mould allergens are very few. Among several hundred patients Bernton et al. (6) found four with marked skin sensitivity to *Cladosporium*. "Desen-

sitization" resulted in satisfactory alleviation of symptoms in three of four patients. Tuchinda & Chai (24) treated six asthmatic children with *Alternaria* antigen and obtained significantly decreased bronchial sensitivity. No evidence, however, of clinical or medication improvement was published. Goldstein & Chai (11) performed rush immunotherapy with various moulds in four patients with childhood asthma. Bronchial challenge tolerance was increased in two subjects and unchanged/decreased in two. Metzger et al. (18) reported a decrement in late asthmatic response in six patients treated with *Alternaria*. The early asthmatic response was reduced significantly in only one subject. The lack of extensive immunotherapy studies with mould allergens is probably caused by the problems involved in producing proper mould

allergen extract (4, 21) and the difficulty in identifying clinically relevant moulds (1, 15). The tremendous work of investigating and standardizing allergens from the mould species *Cladosporium herbarum* has been carried out by Aukrust (5, 22) using highly specific qualitative and quantitative immunological procedures. The availability of a partially purified, biologically standardized extract of *Cladosporium* initiated the study of the diagnosis and immunotherapy of mould allergy.

This placebo-controlled, double-blind study reports the clinical efficacy of immunotherapy with *Cladosporium* estimated by daily symptom score and side effects in patients with a well-documented allergy to *Cladosporium* (17).

MATERIAL AND METHODS

Patients

The patients were selected by screening 62 adults for mould allergy on the basis of a history of exacerbation of asthma in the late summer months (*Cladosporium* peak season) (15). Twenty-five patients showed a positive result in bronchial challenge test (BPT) (16). The clinical relevance of mould allergy was further evaluated by detailed registration of subjective asthma symptoms, consumption of antiasthmatic medication and peak flow measurements during 11 weeks in the 1981 peak *Cladosporium* season (17). Twenty-three patients gave their informed consent to participate and 22 patients completed the first year of immunotherapy. The study was approved by the local Ethics Committee.

All patients included had asthma symptoms of a severity that justified immunotherapy, i.e. asthma symptoms not controlled by medical treatment. Moulds were considered the clinically most important allergens, as patients were either symptom-free (the majority) or had only minimal asthma outside the *Cladosporium* season. Pregnancy, chronic cardiovascular, cardiopulmonary or immunological diseases, and previous immunotherapy with mould within the last 2 years resulted in exclusion from the study. For clinical data of patients completing

the first year, see Table 1. Most patients were allergic to other allergens but *Cladosporium* was considered the most important. Asthma was defined as recurrent episodes of reversible bronchial obstruction, either spontaneously or due to a bronchodilator (2).

According to sensitivity of BPT and skin prick test (SPT) the patients were randomized to treatment with either *Cladosporium* or placebo.

Allergen extracts

A lyophilised, partially purified and biologically standardized preparation of *Cladosporium herbarum* (Pharmalgen®, Pharmacia, Uppsala, Sweden) was used for immunotherapy and *in vivo* tests. To prevent degradation of activity, extracts were reconstituted immediately before use in albumin diluent (0.03 % human albumin in saline) in the concentrations 100, 1,000, 10,000 and 100,000 BU/ml (biological units:

Table 1

Clinical data of patients in the *Cladosporium* immunotherapy trial. No significant difference between the parameters of the two groups was found

	Placebo	<i>Cladosporium</i>
Number	11	11
Sex		
female	2	4
male	9	7
Age (years)	31 16-54	25 17-43
Duration of mould allergy (years)	24 3-40	16 8-40
Exclusively mould allergy	2	1
Allergy to other moulds		
<i>Penicillium</i>	4	5
<i>Aspergillus</i>	4	5
SPT > + + +		
<i>Mucor</i>	1	4
<i>Candida</i>	5	6
<i>Alternaria</i>	9	8
Associated allergies		
pollen	7	8
SPT > + + +		
animal dander	7	9
mites	3	7

Median and range.

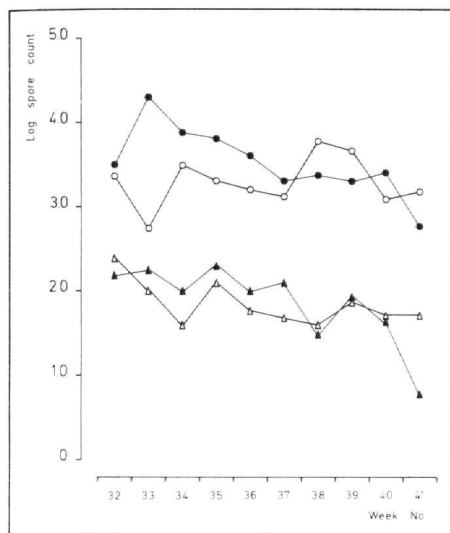


Fig. 1. *Cladosporium* spore counts during a 10-week observation period in the 1981 (○) and 1982 (●) peak mould season. Spore counts of the second dominating spore, *Alternaria*, are also evident, 1981 (△), 1982 (▲).

1,000 BU = 1 HEP). Caramelized histamine HCl 0.01, 0.03, 0.1 mg/ml, labelled in random order like the *Cladosporium* extract, was used as placebo.

Spore counts

Daily spore counts were obtained by a BIAP sampler and data published by the Danish Aerobiological Group (31). The spore counts of the two dominating species (*Cladosporium* and *Alternaria*) in the registration periods 1981 and 1982 are shown in Fig. 1.

Symptom score

All patients completed daily symptom scores during corresponding 10-week periods in 1981 and 1982. The severity of asthma was assessed by registration of asthma day and night and cough + sputum, each scored 0–3. Peak flow was obtained mornings and evenings and the highest of three recordings was noted. Anti-

asthmatic medication was kept to a minimum to avoid complete disappearance of asthma symptoms due to over-medication. The basic treatment was inhaled beta-2-agonist supplemented with slow release theophylline, oral beta-2-agonist or beclomethasone aerosol. Severe symptoms were relieved by systemic prednisolone. Missing data were handled as previously described (17).

Study design

Pretreatment symptom score was obtained in the 1981 peak *Cladosporium* season (August to mid October). *In vivo* tests and blood sampling were carried out in February 1982 and immunotherapy was initiated in March 1982. The clinical efficacy of immunotherapy was evaluated in the 1982 *Cladosporium* season, i.e. after 5–7 months of treatment. The clinical efficacy was assessed for each patient by comparing symptom score (asthma + peak flow score), medication score and the combined (total) score obtained in the two seasons. Thus the patients served as their own controls. Clinical improvement/deterioration was assessed semiquantitatively to avoid interference of varying spore counts during the two seasons, and to ensure that changes in clinical state were not caused by changes in spore counts but initiated by immunotherapy. Arbitrary "improvement" in symptom score was considered significant, if the mean daily asthma score (scored 0–3) was reduced by one score and/or peak flow increased 25 l/min. "Deterioration" was the inverse change, and "unchanged" symptom score was registered if asthma score and peak flow changed less than stated above or changed in either direction. Medication score was "improved" in the case of a reduction in mean daily drugs consumption of one therapeutic dose, i.e. 2 puffs of beta-2-agonist, 2.5 mg of oral terbutaline, 300 mg of sustained release theophylline, 4 puffs of beclomethasone (200 µg) and 2.5 mg of prednisolone. Discordant changes in drug consumption were evaluated according to the relative changes. The overall clinical status was considered "improved"

provided that symptom score and/or medication score were improved. Complementary changes were regarded as "deterioration", and if the clinical score was improved and medication aggravated or vice versa the clinical status was "unchanged".

The absolute severity of the asthma disease (17) in the entire pretreatment registration period was assessed for each patient. The mean sum of the daily subjective registration of asthma symptoms (asthma day and night, and cough + sputum) each graded 0-3 was used. Peak flow reduction in the *Cladosporium* season was calculated in per cent of the maximum value observed for each patient outside the season and scored one point for each 10% reduction. Medication was scored in the following way: 1 point for every 2 puffs of beta-2-agonist aerosol, 2.5 mg of oral terbutaline, 300 mg of sustained release theophylline (Theo-Dur®), 4 puffs of beclomethasone and 2.5 mg of oral prednisolone. The sum of mean asthma score, mean peak flow score and medication score represents the total severity of asthma disease and was used in the calculation of

correlation of diagnostic test sensitivity and severity of disease.

Immunotherapy

Immunotherapy was performed in an out-patient allergy clinic using a clustered regimen during the dose-increase phase. The regimen was scheduled to four visits with five injections per visit and clusters given every fortnight. Treatment was initiated with 10 BU and the dose increased as shown in Table 2. The scheduled top dose was 100,000 BU or the maximally tolerated dose, i.e. one step reduction of the dose eliciting repeated mild systemic reactions. Maintenance dose was given once monthly with a modest reduction during the mould season. Patients were asked to notice local reaction (swelling) within the first few days. Systemic and local reactions within 30 min of injection were registered in the clinic. Local swelling exceeding 5 cm and/or systemic reaction during the dose-increase phase resulted in reduction of the following dose.

Table 2

Immunotherapy schedule for dose-increase phase

Cluster No.	Injection No.	Dose BU	Cumulative dose BU
I	1	10	10
	2	50	60
	3	100	160
	4	300	460
	5	500	940
II	6	500	1460
	7	800	2260
	8	1000	3260
	9	2000	5260
	10	4000	9260
III	11	4000	13260
	12	6000	19260
	13	8000	27260
	14	10000	37260
	15	20000	57260
IV	16	20000	77260
	17	40000	117260
	18	60000	177260
	19	80000	257260
	20	100000	357260
	21	100000	457260
	22	100000	557260

Statistics

Differences between placebo group and *Cladosporium* group were evaluated by Mann-Whitney U-test. Correlations were made by Spearman's Rho, and clinical efficacy calculated by a Chi-square test.

RESULTS

Pretreatment assessment

The patients were randomized to either placebo or *Cladosporium* treatment according to BPT and SPT sensitivity. As is evident from Fig. 2 there was no statistically significant difference between the two groups. The same holds for pretreatment asthma severity except in the case of peak flow, which was significantly ($P < 0.05$) lower in the *Cladosporium* group (Fig. 3). This figure furthermore shows that the *Cladosporium* group has slightly more symptoms than the placebo group. No difference between the two

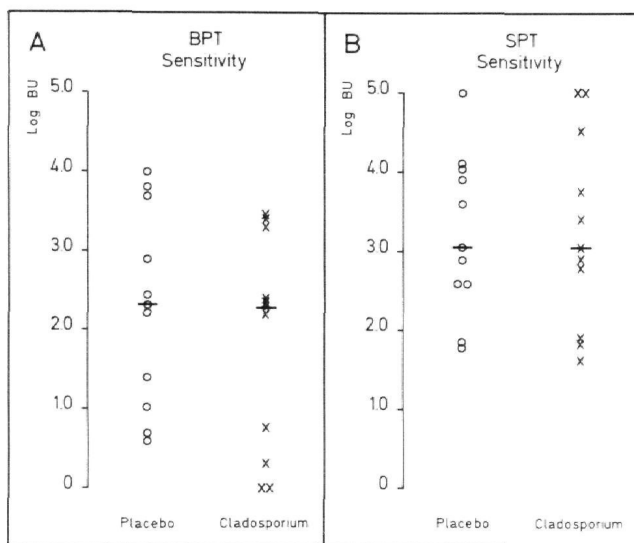


Fig. 2. Pretreatment bronchial provocation test (BPT) and skin prick test (SPT) sensitivity of placebo (○) and *Cladosporium* (X) treated patients. Median values are marked. No statistically significant difference between the two groups was found.

groups concerning sex, age or skin reactivity to other inhalants was found (Table 1).

Immunotherapy

Ninety-six per cent of the patients completed the first year of the study. Only one patient in the *Cladosporium* group dropped out due to family problems.

All patients in the placebo group reached the

scheduled top dose (100,000 BU). The mean top dose in the *Cladosporium* group was significantly lower (46,000 BU, $P < 0.001$) and only one patient received a dose of 100,000 BU. Due to systemic side effects the maintenance dose was further reduced to 18,000 BU (Table 3). The mean cumulative dose preseasonally and after 1 year of treatment in the *Cladosporium* group is evident from Table 3. Typical examples of the dose-increase phase of a placebo and *Cladosporium* treated patient, including local and systemic reactions, are shown in Fig. 4.

Table 3
Dosage of allergen

Dosage of allergen	Biological Units
Maximum top dose	46,000 10,000-100,000
Maintenance dose	18,000 5,000-60,000
Cumulative dose (preseason)	235,000 71,000-521,000
Cumulative dose (1-year treatment)	444,000 146,000-1,621,000
Mean and range.	

Table 4

Number of visits (clusters) and injections per cluster during dose-increase phase

	Placebo	<i>Cladosporium</i>	
Number of patients	11	11	
Visits (clusters)	4.1 4-5	5.2 3-8	*
Injections/cluster	4.9 4-5	3.7 2-5	**

Mean and range. * $P < 0.02$. ** $P < 0.001$.

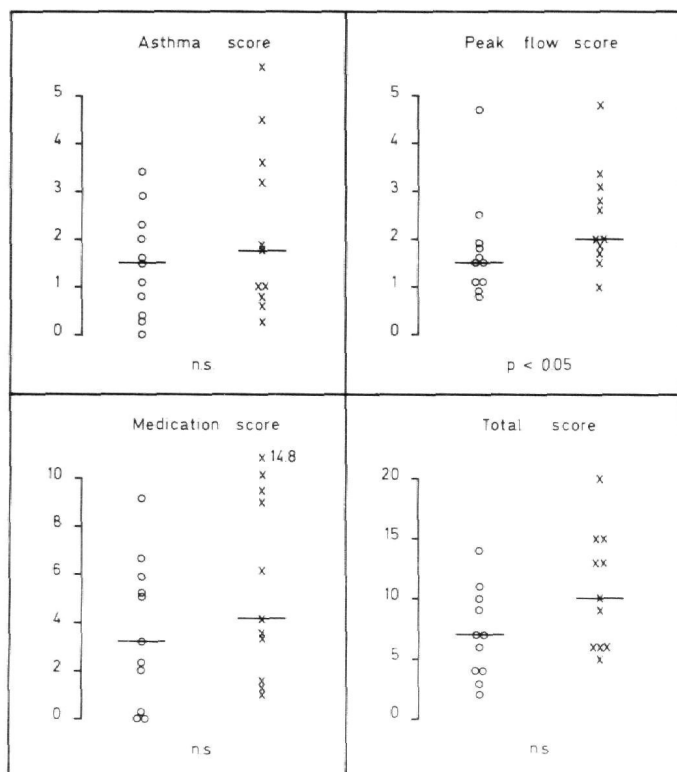


Fig. 3. Symptom score-based evaluation of pretreatment severity of asthma of the placebo (O) and *Cladosporium* (X) group (for further details of score calculations see text). Median values are shown. n.s. = not significant.

In spite of the fact that the maximally tolerated dose in the *Cladosporium* group was only about half of that reached in the placebo group, the *Cladosporium* group needed an additional visit (cluster) to the scheduled four to reach the top dose (Table 4). The *Cladosporium*-treated also tolerated only 3.7 injections per cluster compared with 4.9 in the placebo group (Table 4).

Both the maximally tolerated and the 1 year cumulative doses were inversely associated to the pretreatment asthma severity (score system), but the correlation did not achieve significant levels (Fig. 5).

Clinical efficacy

As seen from Fig. 1 *Cladosporium* spore count in 1982 exceeded the 1981 count in seven out of a 10-week observation period. The semiquantitative assessment of "improved", "unchanged" and "deteriorated" symptoms, medication and overall scores of the placebo and *Cladosporium* group is shown in Table 5. A statistically significant difference was not found in either symptom or medication score, but the combined (total) evaluation with respect to clinical efficacy showed a significant ($P = 0.03$) difference in favour of *Cladosporium* immunotherapy. "Improvement" of asthma was found in

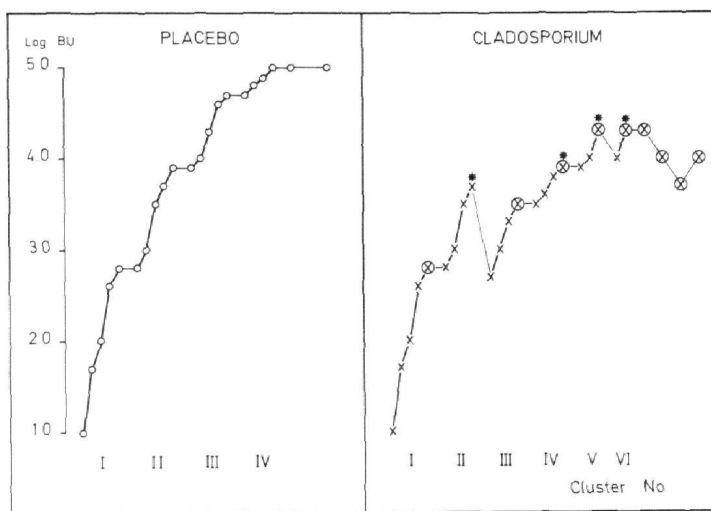


Fig. 4. Examples of a typical course of the dose-increase phase in placebo (O) and *Cladosporium* (X) treated patients. ⊗ = delayed local reaction > 8 cm and * = immediate systemic reaction.

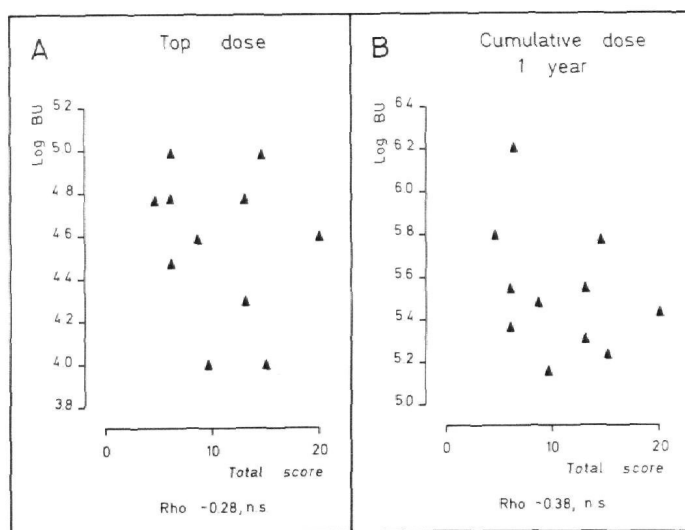


Fig. 5. Relation between the maximally achieved top dose in dose increase phase (A), the 1-year cumulative dose (B), and the pretreatment severity of asthma (total score) in the *Cladosporium* group (for further details of score calculations, see text). n.s. = not significant.

45% of the *Cladosporium* group versus 9% in the placebo treated. "Unchanged" clinical symptoms were found in 36% (*Cladosporium*) and 18% (placebo) and "deterioration" in 18% versus 73%, respectively. Regarding "improvement" two patients in the *Cladosporium* group improved in both scores and three in either symptom or medication score versus none and one in the placebo group, respectively. Aggravation of both scores was found in three patients in the placebo group versus 0 in the *Cladosporium* group and in only one of the scores in five and two patients, respectively.

The 2-3 times higher spore counts in the 1982 season might justify the simplification that unchanged symptoms are regarded as clinically improved disease. Using this approach a clinical efficacy was found in 27% of placebo-treated versus 81% in the *Cladosporium* group ($P = 0.01$).

Side effects

The high-dose immunotherapy regimen implied a higher frequency of side effects occurring primarily during the dose-increase and seldom at maintenance dose. As shown in Table 6, almost all side effects were observed in the *Cladosporium*

group. Delayed local reaction (swelling at the injection site of more than 8 cm in diameter within the first 2 days) occurred in 58% of the clusters, and systemic reactions in 74%. The corresponding figures in the placebo group are 0 and 4%. All the *Cladosporium* treated patients experienced one or more systemic reactions and 73% had a delayed local reaction. No delayed local reactions and only two episodes of immunotherapy-induced asthma in one patient was observed in the placebo group.

Systemic side effects were mostly asthma: 32 episodes of mild asthma (treated with a beta-2-agonist aerosol) and 27 severe attacks (requir-

Table 6

Delayed local and systemic side effects during dose-increase

	Placebo	<i>Cladosporium</i>	
Delayed local reactions/cluster	0	0.58 0-1.0	***
Delayed local reactions/injection	0	0.15 0-0.35	***
Systemic reactions/cluster	0.04 0-0.4	0.74 0.4-1.0	***
Systemic reactions/injection	0.01 0-0.1	0.21 0.13-0.25	***

Mean and range. *** $P < 0.001$.

Table 5

Clinical efficacy of *Cladosporium* immunotherapy evaluated by changes in symptom-, medication-, and total score in a 10-week period in 1982 compared with the corresponding 1981 period. For definition of "improved", "unchanged", and "deteriorated" see text

	Improved	Unchanged	Deteriorated
Symptom score			
Placebo	0	6	5
<i>Cladosporium</i>	4	5	2
		$P = 0.07$	
Medication score			
Placebo	1	4	6
<i>Cladosporium</i>	5	4	2
		$P = 0.10$	
Overall score			
Placebo	1	2	8
<i>Cladosporium</i>	5	4	2
		$P = 0.03$	

Table 7

Systemic reactions in the *Cladosporium* group

	Total	Mean/ patient	Range
Asthma			
Mild (treated with aerosol)	32	2.9	1-6
Severe (requiring inhalation of beta-2-agonist)	27	2.5	1-5
Delayed asthma (24 h)	5		
Anaphylactic reactions			
Status	1 patient		
Angioedema	1 patient		
Urticaria + hypotension	1 patient		
Other side effects			
Headache	1 patient		
Depression	1 patient		

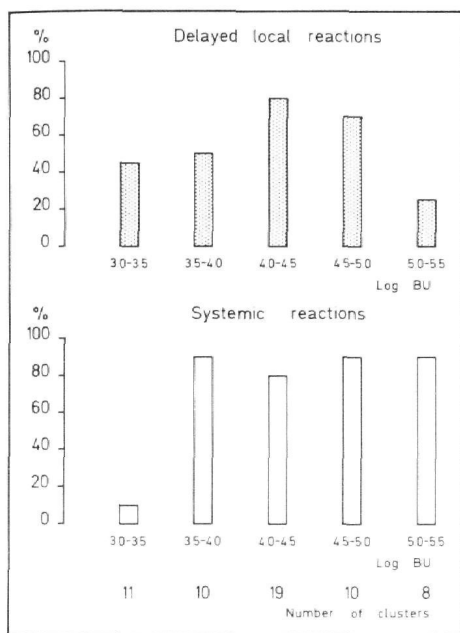


Fig. 6. Relation between the actual dose delivered at each cluster and the percentage of patients reacting with delayed local reactions (> 8 cm swelling within 24 h of injection) and immediate systemic reactions. The number of clusters associated with the doses is also stated.

ing inhalation of nebulized beta-2-agonist), were observed within 30 min of injection (Table 7). Five patients experienced delayed asthma (within the first 24 h of injection). Both immediate and delayed asthma responded well to medical treatment and in no case was hospitalization indicated. During the dose-increase phase anaphylactic reactions were observed in three patients (27%): one case of status asthmaticus, one of angioedema and one patient with generalized urticaria with complicating hypotension. These patients were all hospitalized for a 24-h observation period. Other uncommon side effects were one patient complaining of headache in connection with the injections and one patient with depression subsequent to immunotherapy. These side effects disappeared during the course of maintenance treatment.

The relation between the frequency of de-

layed local and systemic reactions and the actual dose of allergen administered at each cluster is shown in Fig. 6. The highest number of local reactions was found in the dosage range 10,000–100,000 BU (80 and 70%, respectively) and the least number (25%) with doses exceeding 100,000 BU. Systemic reactions were distributed almost uniformly over the dose range 3,000 to 300,000 BU amounting to 80–90%.

The capacity of a delayed local reaction at the previous cluster to indicate a systemic reaction was evaluated by dividing the local reactions into two groups: $>$ and < 8 cm and relating them to the reaction in question. Nineteen/21 (90%) cases of systemic reactions were preceded by a local reaction < 8 cm and 25/28 (89%) by a local reaction > 8 cm. Systemic reactions were observed in patients with no local reaction at all at the previous cluster, while few patients with local reactions amounting to 20 cm experience no systemic reaction.

The relation between the pretreatment estimate of asthma severity (score system) and local and systemic reactions is illustrated in Fig. 7. Only local reactions were significantly correlated to the pretreatment asthma score.

DISCUSSION

Pretreatment severity of disease

When evaluating the clinical efficacy of immunotherapy, especially in studies including small numbers of patients, several factors are crucial. First and foremost, the patients in the placebo and actively treated groups must be properly matched (3). In the present study patients were randomized according to SPT and BPT estimated degree of allergy. The clinical efficacy of *Cladosporium* immunotherapy reported in this paper is reinforced by the finding of only slightly more severe asthma disease in the *Cladosporium* group compared with the placebo group. Only as regards peak flow was a significantly increased disease activity found in the *Cladosporium* group. Furthermore, an equal distribution of allergy to other inhalants, age,

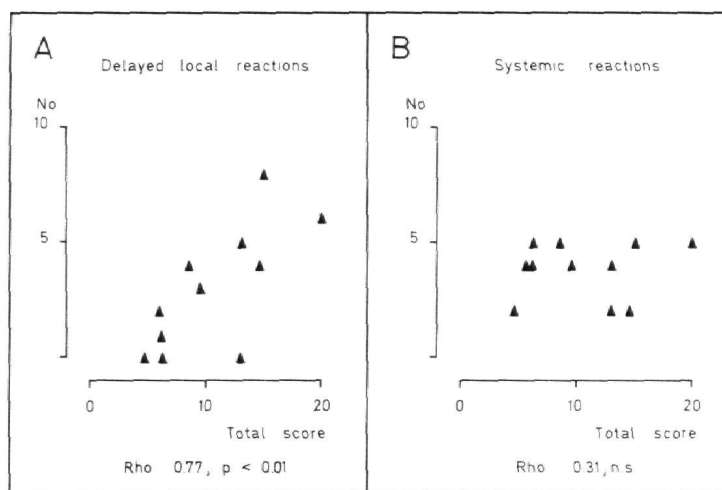


Fig. 7. Number of delayed local (A) and systemic reactions (B) per patient during dose-increase related to the pretreatment severity of asthma (total score) (for further details of the score calculations, see text). n.s. = not significant.

sex and duration of allergy to the allergen in question is crucial (3). The possibility of patients "growing out" of their asthma does not seem a plausible explanation, as the patients have had mould-induced asthma for a minimum of 3 years with median value of approximately 20 years (3).

The optimal material for evaluation of the clinical efficacy of immunotherapy would be monoallergic patients. As regards asthma especially mould asthma, this is almost impossible and the present study only includes one monoallergic patient in the *Cladosporium* group and two in the placebo group. The influence of pollen allergy was partly avoided by registration only at the termination of the mould spore season (17). Grass pollen and mugwort were only present in the first few weeks and did not influence the entire period. A possible interaction of allergy to animal dander could not be excluded, but no patients had daily contact with animals known to cause symptoms. Allergy to mites might be responsible for increased symptoms in the last weeks of the observation period, but, as pointed out in the diagnostic study (17), this does not seem clinically relevant.

Relevance of *Cladosporium* allergens

The relevance of the examined allergens in eliciting symptoms is a prerequisite to obtaining a therapeutic response (3, 8). The role of *Cladosporium* in the patients involved has been extensively documented (16, 17). The relevance of the antigenic composition of the *Cladosporium* extract employed in the present study was shown by crossed radioimmunoelectrophoresis (16). The same batch was used throughout the study. Likewise, the same preparation was used for diagnosis and immunotherapy, and the potency (allergenic activity) was controlled by crossed immunoelectrophoresis.

Immunotherapy

To improve patient compliance the clustered dose-increase schedule was chosen because of convenience in reducing the number of visits before reaching maintenance dose (10, 26) compared with conventional immunotherapy (1 or 2 injections per week). Related to the scheduled regimen (Table 2) the actively treated patients needed one additional visit to reach maintenance

dose, but tolerated one less injection per cluster (Table 4). In spite of this difference the mean maintenance dose in the *Cladosporium* group was less than 1/5 of that of the placebo group (Table 3). The high dose immunotherapy was based on the observation of the Baltimore group (26) that doses resulting in untoward reactions are necessary for optimal relief of symptoms.

The pretreatment degree of asthma severity could be suspected of influencing whether the scheduled top dose was reached or not. However, neither the maximal dose delivered at each cluster nor the 1 year cumulative dose was significantly associated with the total asthma score (Fig. 5). Thus the allergen dose may be influenced by other factors.

Clinical efficacy

Only one placebo-controlled trial has shown clinical efficacy in mould-allergic children (9). The present study is the first to document a therapeutic efficacy in adults. Contrary to the paediatric study, that failed to show a significant improvement during the "entire" mould season (a 10-week registration period) but only in the 2 weeks with highest spore counts (9), our evaluation is based on a whole 2½ month observation period. Due to the unknown effect of registration over two mould seasons with different spore counts and some minor changes in the anti-allergic medication, we did not use a score system to evaluate the clinical efficacy. The obvious disadvantage of the small number of patients in each group is partly compensated by using the patient as his own control and thus using individual changes in each group contrasting to group differences. Registration during the season prior to immunotherapy supplies the advantage of objective registration of disease severity and relevance of the offending allergen. Furthermore, it prevents the pitfall of individual differences in the subjective scoring of symptoms and in the individual attitude to taking drugs and the responsiveness to drugs. Studies relating symptom and drug scores in the placebo and actively treated group during only one season might lead to false conclusions (3, 20).

The relative role of improvement in symptom

score and reduction in antiallergic medication in evaluating the clinical efficacy of immunotherapy might be questioned (27, 28). In the present study we have evaluated semiquantitative changes in both symptom score (asthma + peak flow) and medication consumption without demonstrating a significant difference between placebo and *Cladosporium* treated patients. The combination of symptom and drug consumption, however, elucidated a significant clinical efficacy of *Cladosporium* immunotherapy (Table 5). As changes in symptom score might be a consequence of altered medication only or, on the contrary, a reduction in medication might result in increased symptoms, this approach seems justified. The total clinical state of the patient is, however, a result of the combination of clinical symptoms and drug consumption. This semiquantitative assessment prevents false conclusions based on the relative weight of symptom and medication. Thus "improvement" was a consequence of either improvement in symptoms or medication or improvement in both parameters. "Unchanged" clinical score represents either unchanged in both assessments or one improved and one deteriorated.

Unchanged symptoms in the 1982 season compared with 1981 cannot *per se* be considered as improved clinical asthma, but due to the considerably higher *Cladosporium* spore count in 1982 patients experiencing no aggravation might be regarded as improved. Thus a clinical efficacy of 80% in the *Cladosporium* group compared with 30% in the placebo group corresponds to figures found in a number of studies (20).

Side effects

The lower allergen dose achieved in the *Cladosporium* group is a clear consequence of the high frequency of side effects. Although it is possible that immunotherapy regimens involving more injections over a longer period might save patients from some systemic reactions, the clinical advantage of an aggressive dose increase regimen was found worth investigating. Furthermore, due to the lack of information concerning clinical efficacy and the possibility of

type III reactions (13) an unaltered *Cladosporium* extract was used. Other studies employing depot or modified extracts have shown a reduced frequency of immediate allergic reactions (12, 30).

During the dose-increase phase more than half of the clusters were complicated by delayed local reactions larger than 8 cm and three out of four patients experienced systemic reactions at each cluster. All *Cladosporium* treated patients had one or more systemic reaction in contrast to only one placebo-treated with two episodes of systemic side effects. No delayed local reaction was observed in the placebo treated patients. This significant difference in the frequency of side effects clearly demonstrates the difficulties in performing double-blind studies. The validity of the clinical efficacy is, however, solid, as the results were evaluated without knowledge of allergen doses and side effects and before breaking the code.

As expected in asthmatic patients, most side effects were episodes of bronchial obstruction. The occurrence of systemic side effects within 30 min of injection, i.e. while the patient is still in the ward where therapy can be immediately initiated, is one of the advantages of using aqueous allergen extracts. Only five (8%) of asthmatic attacks were of delayed type and all were managed by patient self-medication. A rather high frequency of severe (anaphylactic) side effects using aeroallergens was found. This is probably a consequence of the high potent doses given and the injection regimen, but is comparable to *Hymenoptera* immunotherapy (23, 29). The high frequency of systemic side effects, even though only a few were potentially life-threatening, limits this treatment to highly specialized clinics. However, provided that appropriate precautions are taken to treat side effects, we consider the risk acceptable when the severity of the disease is taken into consideration. Furthermore, it is worth noting that no patients dropped out due to side effects. No unwanted side effects of type III reactions were observed in the present study (13).

In most studies the occurrence of side effects is related to the highest allergen doses (10, 19, 23, 26, 30). Concerning local reactions this also partly holds for the present study (Fig. 6), but

systemic side effects were observed almost uniformly over a two-log-step dosage range (3,000–300,000 BU). Consequently, only the very low allergen doses can be injected without a high risk of eliciting systemic reactions. Systemic side effects could be predicted neither by a previous large local reactions (30), nor by the pretreatment severity of asthma. The significant correlation between local reactions and asthma score is only of limited clinical relevance as local reactions probably represent a beneficial immunological response to allergen injections.

In conclusion, this double-blind trial is the first to demonstrate a significant clinical efficacy of immunotherapy with a mould extract (*Cladosporium*) in a placebo-controlled study in adult asthmatics. The clinical efficacy was evaluated by a combination of subjective (asthma scoring) and objective (peak flow and medication consumption) parameters over a 10-week period including approximately half of the *Cladosporium* season. A frequency of 100% systemic side effects in the *Cladosporium*-treated is a consequence of the high doses of potent allergen extract and the clustered dose-increase regimen. Considering the severity of the disease we believe the risk acceptable provided necessary precautions are taken to treat side effects. Data concerning the relation between clinical efficacy, allergen dose and SPT, BPT, RAST and IgG-response are in progress.

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