

A Prospective Study on the Safety of Immunotherapy in Children with Severe Asthma

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One hundred and six of 503 (21%) consecutive children with asthma, who from 1979 to 1983 commenced hyposensitization therapy, were prospectively studied on the safety of immunotherapy. More than 80% of the patients completed therapy without side effects. Thirteen patients were withdrawn from hyposensitization due to moderate and predictable, but intolerable, side effects such as asthma/rhinitis, urticaria and subcutaneous nodules and hypersensitivity to aluminium. However, more alarming was the outcome in six children, who after an uneventful course of immunotherapy and after several months on maintenance therapy, suddenly, 5 to 20 min (mean 10 min) following an earlier tolerable allergen injection, developed severe, anaphylactic reactions, in three of them nearly fatal. Mould extracts were responsible for the most frequent and serious side effects (*Alternaria iridis/alternata*, 3 patients, *Cladosporium herbarum*, 8 patients). Furthermore, serious, but not immediately life-threatening, anaphylactic reactions occurred in two children treated with *Phleum pratense*. On the other hand, hyposensitization with *Dermatophagoides pteronyssinus* was very well tolerated.

Key words: immunotherapy; side effects allergen extracts; asthmatic children.

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In selected patients with IgE-mediated asthma/rhinitis, not sufficiently treated with beta₂-agonists, inhaled steroid or theophyllin preparations, hyposensitization therapy with allergen extracts offers a useful alternative. An anaphylactic reaction, although rare, is always a potential threat following an allergen injection. On the other hand, warning signs such as aggravation of asthma or the development of urticaria while on increasing allergen doses, often precede anaphylactic reactions (6). In a minority of patients, however, such warning signs do not occur.

In a prospective study, evaluating possible side effects, we observed unpredictable, nearly fatal reactions in six patients on maintenance therapy with mould or grass pollen extracts. In another 13 patients, hyposensitization was stopped due to less pronounced but intolerable side effects.

PATIENTS AND METHODS

Five hundred and three children with IgE-mediated asthma were consecutively studied at The Children's Allergy Clinic, Department of Pediatrics, Aalborg Hospital North, from June 1978 to July 1981. The age range of the patients was 3 to 14 years (median age 9 1/12 years) and the boy/girl ratio was 3/2. All patients were prick tested with the following allergen extracts (ALK, Copenhagen): birch-, grass (*Phleum pratense*)- and artemisia pollen, cat-, dog-, horse-, cow-, rabbit-, hamster- and guinea pig dander, *Dermatophagoides pteronyssinus*, *Alternaria iridis* and *Cladosporium*. A prick test was considered positive if equal to or more than 1 HEP (Histamine Equivalent by Prick). Furthermore, in cases of negative prick tests (< 1 HEP), RASTs (ALK, Copenhagen) to the above mentioned allergens were carried out. A

RAST was considered positive if equal to or more than RAST-class 3. If discrepancy between anamnesis, prick tests or RAST existed in an individual patient, bronchial provocation tests (BPT) were carried out.

Bronchial provocation test

Allergen extracts at concentrations 1:10,000, 1:1000 and 1:200 were used. After each inhalation at the different concentrations, forced expiratory volume in 1 s (FEV_1) was measured repeatedly for 5 min, and if no immediate reaction took place, the next concentration was given, and so on. Following an immediate reaction or no reaction to the top dose, peak expiratory flow (PEF) was recorded hourly for 8 h. The provocation concentration of the antigen required to produce a fall in FEV_1 (immediate) or PEF (late) of 20% or more was considered positive. In the control test, 0.9% saline was inhaled before a BPT with the allergen took place. As a further control, all patients underwent a BPT with an allergen extract to which they were not suspected to be sensitive and all were negative. All medications were withdrawn from the patients 48 h before challenge.

Selection of patients for immunotherapy

After the primary evaluation at our clinic, most patients are started on a treatment schedule with inhaled β_2 -agonists, 2 puffs (200 μ g) 3 or 4 times daily for a month. If this is insufficient (> 2 attacks of asthma a fortnight and/or a FEV_1 of $< 70\%$ of predicted) inhaled steroids (200 μ g, 2 times a day) for another month are added. If still not sufficiently treated (> 2 attacks of asthma a month and/or a FEV_1 of $< 70\%$ of predicted), a slow-release theophyllin preparation, 15–20 mg/kg/day is added. On this treatment combination, the patients are evaluated 3 times or more per year.

However, even on the above-mentioned treatment schedule, an estimated 20% of our asthmatic patients still suffer impressive attacks of asthma (> 1 attack a month in perennial asthma and > 1 attack a week in seasonal). In such patients, our clinic recommends parents

to have their child hyposensitized with the most offending allergen.

Following these criteria, 106/503 (21%) of the present patients were hyposensitized during 1979 to 1983. Seventy-two (68%) were hyposensitized by their general practitioners, the remainder at our clinic. The family doctors were requested to contact the clinic if anything unexpected happened during hyposensitization. In the event of this, the patients were referred to us for further treatment, and the final decision to stop immunotherapy in an individual because of intolerable side effects was always taken by one of the senior doctors at the allergy clinic.

Finally, 91% and 9% were hyposensitized with allergen extracts respectively purchased from ALK, Copenhagen or Dome-Hollister-Stier, England.

RESULTS

Among the 503 asthmatic children, the most common allergens responsible for asthma were housedust mite (52%), animal danders (29%), pollen (20%) and moulds (14%). This is in agreement with previous results obtained among Danish children with IgE-mediated asthma (15). Allergy to pollen and animal dan-

Table 1

Allergy diagnosis in 503 asthmatic children obtained by anamnesis, prick tests, RAST and bronchial provocation

	Pollen	Animal dander	House-dust mite	Moulds
Anamnesis + prick	51	30	31	5
Prick test + RAST	22	85	121	29
Bronchial provoc.	28	331	110	37
Total	101	146	262	71

Table 2

Allergen extracts used for immunotherapy in 106 asthmatic children

	<i>Phleum pratense</i>	<i>Dermatophagoides pteronyssinus</i>	Cat/dog dander	Moulds
No. patients (%)	20 (19)	38 (36)	22 (20.8)	26 (24.5)

ders was easily diagnosed by anamnesis, prick test and RAST, whereas allergy to housedust mite and moulds in many instances could only be obtained by BPT (Table 1).

It appears from Table 2 that in accordance with the frequency of the different allergies, most children commenced immunotherapy with housedust mite, cat- or dog dander and grass pollen extracts. However, although only a minority of the patients had mould allergy, a substantial number were put on treatment with mould extracts. This was done because allergy to moulds often causes severe and protracted courses of asthma in children, in many instances necessitating the use of peroral steroids (14).

According to most manufacturers, the recommended period on maintenance therapy is

approximately 3 years. At the "running-out" period in 1985, sufficient data for evaluating the course of immunotherapy were available for 102/106 (96%) of the patients. Three patients had stopped hyposensitization themselves and one patient had moved out of the area (two commenced treatment with housedust mite, one with cat dander, and one with grass pollen).

As seen from Table 3, 73/102 (72%) of the patients had completed immunotherapy without side effects, and 10 patients (10%) were still on maintenance therapy without problems. However, 13 children, due to moderate, but intolerable, side effects, were withdrawn from treatment. Ten of these children were evaluated at the clinic. However, even a 10- to 20-fold reduction in allergen doses resulted in severe

Table 3
Course of immunotherapy in 102/106 asthmatic children

Allergy	Therapy completed without side effects	Still on maintenance therapy	Withdrawal due to moderate side effects	Withdrawal due to serious side effects
<i>Dermatophagoides pteronyssinus</i>	33	2	1	0
Dog dander	10	2	1	0
Cat dander	4	2	2	0
<i>Alternaria</i>	9	1*	2	1
<i>Cladosporium</i>	4	1*	5	3
<i>Phleum pratense</i>	13	2	2	2
Total	72	10	13	6

* Later withdrawn from therapy due to side effects from the mould extracts.

Table 4
Clinical data in the six asthmatic children who experienced anaphylactic reactions while on maintenance therapy

Subjects	Sex	Duration of asthma (years)	Age (years) at hyposensitization	Allergen extract	Manufacturer	On maintenance therapy (months)	Other allergies	Month when reaction took place
T. L.	F	11	13	<i>Phleum pratense</i>	Dome-Hol-lister-Stier	12	none	January
J. B.	M	5	8	<i>Alternaria alternata</i>	ALK	9	<i>Cladosporium herb.</i>	March
U. C.	M	4	7	<i>Cladosporium herb.</i>	ALK	14	none	February
M. J.	M	7	8	<i>Cladosporium herb.</i>	ALK	9	<i>Alternaria alternata</i>	July
G. G.	M	10	11	<i>Cladosporium herb.</i>	ALK	12	none	February
T. C.	M	13	11	<i>Phleum pratense</i>	Dome-Hol-lister-Stier	8	none	November

asthma attacks, in four patients necessitating hospitalization for several days. Furthermore, dose reduction in three patients who reacted to increasing doses of allergen with severe and generalized urticaria, resulted in a similar reaction, in one patient complicated by Quincke edema. Finally, three patients were withdrawn from hyposensitization due to severely itching nodules on their forearms and the development of hypersensitivity to the aluminium content of the extracts (3). However, in nine children, continuation of immunotherapy was possible, in seven of them with reduced allergen doses.

The clinical characteristics of the six patients who experienced anaphylactic reactions to allergen injections appear in Table 4. All except one (J. B.) were hyposensitized by their general practitioners. Patients U. C., M. J. and G. G., who experienced the most serious reactions, stayed close (3 to 4 min walk) to the hospital intensive care units, and, in spite of adrenalin injections given by their own doctors, all at their arrival to the casualty ward were unconscious with severe wheeze and an unmeasurable blood pressure. They were immediately intubated and treated with intravenous theophyllin, bicarbonate and adrenalin, and all recovered within 2 to 4 days without sequelae.

After a previously tolerated maintenance dose (1.0 ml of highest concentration), patients T. L., J. B. and T. C. experienced severe, although not life-threatening, anaphylactic reactions with wheezing, generalized urticaria, and swelling of the lips and tongue. Within a few minutes, they became dizzy, and their blood pressures dropped from normal to 50–30 mmHg. After immediate treatment with subcutaneous adrenalin injections, the blood pressure rose. In patients T. L. and T. C., wheeze and urticaria subsided within 1 h, and after approximately 10 h observation they were sent home. Patient J. B., however, had a reoccurrence of wheezing and a further drop in blood pressure to 40 mmHg 1 h after the initial event. He was transferred to our intensive care unit and, after 4 days continuous treatment with theophylline infusions and intravenous hydrocortisone injections, he slowly recovered. As seen

from Table 4, the two patients with anaphylactic reactions to grass pollen did not have associated pollen allergies.

Of the 11 patients withdrawn from immunotherapy with mould extracts (Tables 3 and 4), five without side effects were hyposensitized to the highest extract concentration (maintenance dose) at our clinic, using unregistered extracts (ALK, Copenhagen), they then continued immunotherapy under the care of their own doctors. The remaining six patients were hyposensitized by their general practitioners who used registered mould extracts (ALK, Copenhagen).

In all six patients (Table 4) the anaphylactic reactions occurred 5 to 20 min (mean 10–15 min) after the allergen injections; accidentally given i.v. injections were not suspected. Soon after each event, the content, strength and batch numbers of the allergen extracts were checked but there was nothing to remark. Furthermore, none of the side effects occurred in connection with changing of batches. In addition, the patients with moderate or severe side effects did not show more positive prick tests or RAST, and were not more sensitive at BPT to allergen extracts prior to hyposensitization, than those without side effects. Finally, among the six patients with severe side effects, all except one (M. J., Table 4) had the anaphylactic reaction outside the seasons for airborne pollen and mould spores.

In conclusion, the chief offenders among allergen extracts causing moderate/severe side effects were moulds (42.3%), in particular *Cladosporium herbarum*, followed by grass pollen (20%) and animal danders (13%). However, although the majority of patients commencing immunotherapy received housedust mite extract, only one child (2.6%) was withdrawn from treatment with this extract.

DISCUSSION

The main results of the present study were that 13 patients had to be withdrawn from immunotherapy due to predictive, but intolerable side effects. Furthermore, six stopped therapy because of unexpected and severe anaphylactic reactions

when on maintenance therapy. Most of the latter were hyposensitized with mould extracts.

Several studies have reported on the potential hazard of immunotherapy with allergen extracts. Vervlot et al. (11) found that only 0.1 % of a total of 151,997 injections resulted in systemic reactions, none of them serious. Furthermore, Levine et al. (6), Frost et al. (2), and Østerballe (12) in their series of children and adults undergoing hyposensitization reported only minor problems, in particular in patients on maintenance therapy.

It must, however, be emphasized that the rather high frequency of side effects among the present patients might have been because the majority were suffering from serious asthma relatively resistant to therapy with bronchodilators and inhaled steroids. In such patients, as opposed to patients with milder asthma or seasonal rhinitis, even severe side effects must be expected, both with increasing allergen doses and with a maintenance therapy using high strength extracts.

In the present patients, side effects to grass pollen, animal danders and mould extracts were rather frequent. However, the most serious reactions occurred in patients immunized with moulds, especially *Cladosporium herbarum*. In a previous study (5) evaluating the risks in asthmatic children on maintenance therapy with mould extracts, we found that 19% had to be withdrawn from therapy because of serious type III-like reactions. In addition, these patients exhibited a two- to four-fold increase in circulating precipitating antibodies to the injected extracts. We suggested that this might be due to the formation of circulating immune-complexes (IC). Stendardi et al. (9) reported that about 40% of patients immunized with different allergen extracts developed detectable IC in serum simultaneously with a rise in circulating precipitating antibodies - most common in patients hyposensitized with mould extracts.

On the other hand, neither Kemler (4) nor Stein et al. (10) found evidence of IC in patients with rhinitis or asthma who received immunotherapy with moulds, housedust mite or pollen. Furthermore, in 2/3 of the present patients (G. G. and M. J., Table 4), who experienced near-

ly fatal anaphylactic reactions to *Cladosporium herbarum*, no circulating IC determined by the Cl_q -technique were found on two evaluations approximately 2 h after administration of increased doses of the extract and once on maintenance therapy (unpublished results).

However, if circulating IC are implicated in anaphylactic reactions or type-III reactions, the formation of the former may depend on the purity and standardization of the allergen extracts or the use of combination therapy. Egeskjold et al. (1) and Østerballe et al. (13) reported that patients with multiallergy and asthma, immunized with combined allergen extracts as opposed to patients with rhinitis and only pollen allergy, and treated with purified grass pollen extracts, showed a significant increase in aggregated IgG anti-IgG during immunotherapy. The authors suggested that IgG anti-IgG may be stimulated by the presence of IC, and that purity, amount and/or combinations of allergens might influence the production of IgG anti-IgG.

In our previous study on children hyposensitized with mould extracts (5), the majority of patients with type-III-like reactions was immunized with a mixed extract, which consisted of *Alternaria iridis* and *Cladosporium herbarum*. Hence, in the latter patients, the combination of allergens may have influenced the development of such reactions. The children who participated in the present study received one allergen only.

In our patients, intolerable and serious side effects also occurred in those immunized with allergens other than moulds. However, the most frequent and severe reactions occurred in patients hyposensitized with mould extracts. Although impressive efforts have been made to purify mould extracts for diagnosis and therapy (7, 8), substantial problems still exist. Thus, for the time being, immunotherapy in asthmatic children with mould extracts cannot be recommended, unless carried out under careful control.

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