

Double-blind placebo-controlled study of sublingual immunotherapy with house dust mite extract (D.pt.) in children

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Safety and efficacy of sublingual (sublingual-swallow) immunotherapy (IT) with house dust mite extract were evaluated in 30 children (6–15_{2/3} years of age) over the first 12 months of an ongoing study. The cumulative dose was 570 µg Der p I (five times that administered with subcutaneous therapy). Safety: One patient on active treatment dropped out after 8 weeks because of a subjective feeling of severe weakness, questionably induced by the therapy. Five patients on active therapy and one patient on placebo reported minor local side effects. Efficacy: Pulmonary symptoms were reduced after 12 months in actively treated asthmatics, but this was not consistent with the lack of improvement in bronchial reactivity, skin sensitivity and specific IgG and IgG4 against D.pt. in this group. In patients with rhinitis nasal sensitivity was reduced in the placebo group without concomitant improvement in the nasal symptom score. Specific IgE (D.pt. and D.f.) increased significantly more in the active treatment group after 3 and 12 months. We conclude that sublingual IT over 12 months with the fivefold Der p I dose of subcutaneous IT was well tolerated, but there was no consistent clinical or immunological benefit compared to placebo.

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Subcutaneous injection of increasing doses of certain allergens is a clinically effective therapy for allergic disorders like rhinoconjunctivitis or asthma. As this route of application is inconvenient and is occasionally associated with severe systemic side effects, oral and sublingual immunotherapy (IT) have been evaluated in a number of controlled studies in the last 15 years. The results were contradictory. In 1993 the European Academy of Allergology and Clinical Immunology stated that more conclusive data are required before these application routes can be recommended for treatment (1).

Three modes of application can be distinguished. With oral IT the allergen extract is swallowed immediately as aqueous solution or in enteric coated capsules. Oral IT with aqueous solution is characterized by a peak activity of allergen derived peptides in serum between 30 and 90 minutes after ingestion (2). With sublingual IT the extract is kept sublingually for a certain time before it is spat out (sublingual IT) or swallowed (sublingual-swallow IT). Allergen kept in contact to the sublingual mucosa for 30 minutes is detectable locally up to 30 hours

whereas allergen swallowed immediately completely disappears from the mouth within 12 hours (2).

In children, considering only double-blind, placebo-controlled studies with extracts of quantified allergenic potency and objective clinical and immunological outcome determinations, two studies on oral (3, 4) and one study on sublingual immunotherapy (5) have been performed and published. In one of these studies (3) birch pollen extract and in two (4,5) house dust mite (HDM) extract was used. The major allergen content of the therapeutic extracts was not determined in the two house dust mite studies. Only in one of them domestic allergen exposure was assessed, and then only in terms of semi-quantitative assessment of the guanine content of house dust. We therefore conducted the following study.

Material and methods

Patients

Thirty children (20 males, 10 females; age 6–15_{2/3} years) with mild to moderate asthma ($n=8$), allergic rhinitis ($n=8$) or both asthma and rhinitis ($n=14$)

were enrolled in the study. Asthma was defined according to the International Consensus Report on Diagnosis and Management of Asthma 1992 (6). Allergic rhinitis was defined as chronic recurrent nasal itching or sneezing or rhinorrhea in the absence of a cold. All patients were allergic to *Dermatophagoides pteronyssinus* (*D.pt.*) documented by 1. positive skin prick test (wheal to 50 000 standardized biological units/ml (SBU/ml), equivalent to 26.5 µg Der p 1/ml, at least as large as control reaction to 1 mg/ml histamine dihydrochloride), 2. specific IgE (*D.pt.*) of $\geq$ Class 2 (Pharmacia CAP), 3. positive nasal provocation response to *D.pt.* ($\geq$ 40% flow reduction or 60% increase of nasal resistance to 8000 SBU/ml resp. 4.2 µg/ml Der p 1). None of the patients had previously received immunotherapy with *D.pt.*, none used oral steroids, and none had any other significant illness.

In addition to *D.pt.* and *Dermatophagoides farinae* (*D.f.*) the patients were also tested for allergic sensitization against five other perennial allergens (cat, dog, *Cladosporium herbarum*, *Penicillium notatum*, *Aspergillus fumigatus*), seven seasonal allergens (birch, alder, hazel, timothy grass, mugwort, ribwort, *Alternaria tenuis*) and other furry pets if those were kept at home. Sensitization was defined as specific IgE (sIgE) $\geq$ CAP class 2. None of the patients was sensitized against any of the perennial moulds. One (on active treatment) had sIgE against dog and ten (six active treatment - a, four placebo - p) against cat, but none of the patients kept a cat or dog at home. Patients who kept other pets at home were not sensitized against them. Fourteen (seven a, seven p) were sensitized against one or more seasonal allergens. Evaluation of symptoms and tests before and after 12 months of therapy was performed out of the relevant season of each individual.

The study protocol was approved by the ethics committee of the Universitätsklinikum Carl Gustav Carus, and parents and patients $\geq$ 12 years of age signed informed consent statements before the study started.

Immunotherapy

Subjects were randomized according to a code provided by the manufacturer to receive either a purified whole mite body extract in 50% aqueous glycerol (Allergopharma J. Ganzer KG, Reinbek, FRG) or the vehicle alone over 12 months. Patients were advised to retain the extract sublingually for 3 minutes and to swallow it thereafter. Parents of younger children were advised to give the drops to their children if necessary. In a 3-week build-up phase patients took daily increasing doses from 1–7 drops of a 1:100 dilution of the final preparation in the first week, 1–7 drops of a 1:10 dilution in the second

week, and 1–7 drops of the final preparation in the third week. Maintenance was given as 7 drops on 3 days per week. Empty dropper bottles were recollected and new were distributed every three months.

The Der p I content of the active preparation was 11.9 µg/ml, so one drop ($\approx$ 0.045 ml) contained 0.535 µg. The cumulative dose Der p I in 12 months was estimated to be approximately 570 µg which is approximately fivefold higher than the cumulative dose of subcutaneous immunotherapy for one year.

Neither parents and patients nor nurses and physicians knew whether a patient was receiving verum or placebo until the code was broken after all patients had finished one year of treatment. In one patient who received active treatment the code was broken when he had dropped out after three months of therapy.

Skin prick tests

Before therapy and after 12 months quantitative skin prick tests (QSPT) were performed in triplicate with four serial threefold dilutions of *D.pt.* extract (13 500 - 4 500 - 1 500 - 500 SBU/ml resp. 7.1 - 2.4 - 0.79 - 0.27 µg Der p 1/ml, Allergopharma J. Ganzer KG) and histamine dihydrochloride 0.1% and 1% as positive controls. NaCl 0.9% as negative control solution was tested in duplicate. Wheals were marked after 15 min with a thin waterproof pen. These marks were documented by transfer onto a transparent adhesive tape. All tests were performed by two experienced technicians who were not aware of the content of the test solutions. Wheal areas were measured by planimetry (Digikon planimeter, Kontron - Munich). Median wheal to NaCl had to be smaller than 7 mm², median histamine wheals had to be greater than 3 mm², and the median wheal to histamine 0.1% had to be smaller than to histamine 1%.

Sensitivity was quantified by midpoint titration (7). The median wheals in response to the four concentrations of *D.pt.* and histamine 1 mg/ml were evaluated to determine the allergen dose eliciting a wheal equivalent to histamine 1 mg/ml - histamine equivalent prick (HEP 1). For interpolation we assumed a linear dose-response relation between the 3-logarithms of allergen concentration and the skin reaction (wheal area in mm²). The change in sensitivity after therapy was calculated as log 3 HEP 1 at 12 months minus log 3 HEP 1 at 0 months.

Nasal allergen provocation tests

Reactivity of nasal mucosa was determined before and 12 months after therapy by anterior rhinomanometry during quiet active nasal breathing (Rhino-test MP 500, Elektronik Vertriebs GmbH, Ludwigs-

hafen, FRG). Nasal flow at Δ 150 Pascal choanal-anterior pressure drop was measured before and between 15 and 30 min after 0.08–0.1 ml diluent (NaCl 0.9% + 0.4% phenol), and three serial fourfold dilutions of D.pt. extract (500 - 2 000 - 8 000 SBU/ml resp. 0.27 - 1.06 - 4.2 μ g Der p 1/ml, Allergopharma J. Ganzer KG). Nasal reaction was considered positive if flow was reduced by 40% or more or nasal resistance increased by 60% or more compared to NaCl. In case of a 40% or more flow drop to NaCl (compared to baseline) the test was interrupted and repeated later. Results were expressed as provocative allergen concentration (SBU/ml) that induced 40% nasal flow reduction (PC₄₀ nasal flow), calculated by linear graphic interpolation between the last two steps of provocation testing on a semi-logarithmic scale.

Bronchial histamine provocation test

Bronchial reactivity was determined following the recommendations of Zach (8) with histaminophosphate in phosphate buffer in increasing doubling concentrations from 0.03 up to 8.0 mg/ml. The concentration of histamine (mg/ml) that induced a 20% reduction of FEV₁ (PC₂₀ FEV₁) was calculated by linear graphic interpolation between the last two steps of provocation testing on a semilogarithmic scale.

Serologic parameters

Total IgE and specific IgE and IgG₄ against D.pt. and D.f. were determined before and after 3 and 12 months of therapy by CAP fluorescence enzyme immuno assay (Pharmacia Diagnostics AB, Uppsala, Sweden). IgE-values were expressed as kU/l, IgG₄ values as % of a reference standard of pooled serum from patients with birch pollen allergy after clinically successful immunotherapy. In addition, total specific IgG against D.pt. was determined by a solid-phase radioimmunoassay using I¹²⁵-labelled protein A from *Staphylococcus aureus* (9). Values were expressed as % of a reference standard of pooled serum from patients with grass pollen allergy after clinically successful immunotherapy.

Symptom and medication diary

Patients or their parents kept a diary from 4 weeks before start of therapy until the end of the 12-month-period of therapy. Every day they scored severity of symptoms with 0–3 points separately for different organs and symptom types (eyes: itching, secretion, reddening; nose: sneezing, secretion, nasal blockage; lower airways: cough, wheeze, shortness of breath). In addition they noted other illness

and adverse events, regular and additional medication, and intake of study medication. In order to evaluate the effect of therapy the mean daily symptom scores for each organ in the run-in-phase were compared with those in the twelfth month of therapy.

Physician's and patients' subjective assessment

Before and after 12 months of therapy patients were interviewed and physically examined by a blinded physician (T. H.). Patients' subjective assessments regarding their allergic symptoms were recorded as score from 1 to 10. The physician recorded medication requirements and his summarized opinion regarding the health status (very much improved - improved - unchanged - worse - no decision).

Determination of allergen exposure

Carpets (1 m²) and children's mattresses (1.6 m², under cover) were vacuumed for five minutes with at least 800 W by the inhabitants with their own vacuum cleaner following written instructions. Dust was collected with a sampling device (ALK Denmark) holding a cellulose filter, that retains 85% of particles of 0.7–1.5 μ m size and 90% of particles larger than 1.5 μ m (Filtrak GmbH, No. 60: 0.35 mm thick, pore diameter 30–40 μ m). Samples were weighed and processed unsieved (allergen extraction from dust and filter paper). The concentration of HDM allergens Der p I and Der f I was determined with a commercial sandwich ELISA (ALK, Copenhagen, Denmark). Assay sensitivity was 3 ng/ml or 0.03 μ g/g dust. Results were expressed as allergen concentration (μ g/g dust) and as amount of surface allergen (μ g/m²).

Statistical analysis

Within-subject differences over time were analysed by Wilcoxon Matched-Pairs Signed-Ranks Test. Group comparisons were made with the Mann-Whitney U-Test (numeric data) or the χ^2 -Test (categorical data). If the distribution of numeric data fulfilled the main criteria of normality (symmetric, unimodal), we additionally performed a *t*-test in order to evaluate possible effects with greater sensitivity.

Power analysis: based on the given number of patients and the measured variances calculations were made to estimate the difference of the effects in the treatment versus placebo group that would have been detected with $\alpha = 0.05$ and $\beta = 0.2$. These calculations used power tables for two-tailed *t*-test (10) and were based on the assumption that the U-test yields approximately 90% of the power of a *t*-test.

Table 1. Demographic and clinical characteristics of active and placebo group. The table shows median (min-max) values for age, duration of illness, and Der p 1 exposure and number of patients for gender and diagnosis of asthma and allergic rhinitis

	Active	Placebo
Age (years)	11 _{1/3} (6-15 _{2/3})	9 _{11/12} (6 _{1/12} -14)
Gender (male/female)	10/5	10/5
Asthma only (n)	3	5
Rhinitis only (n)	3	5
Asthma and Rhinitis (n)	9	5
Duration of Asthma (years)	4 _{1/2} (1-10)	2 _{1/2} (0 _{1/12} -7)
Duration of Rhinitis (years)	5 (0 _{1/12} -10)	3 _{1/2} (0 _{1/12} -8)

Results

There were no significant differences between treatment and placebo group in clinical and demographic characteristics and domestic HDM exposure (Tables 1 and 2). *D. pteronyssinus* specific serum IgE levels, skin prick test reactivity, nasal and pulmonary symptom scores and specific nasal and nonspecific bronchial reactivity were not significantly different at study entry. Table 3 shows values at 0 months for organ-specific parameters for the subgroups of rhinitics and asthmatics only. There were no active-placebo differences for these parameters, either, when all patients were considered. There were no significant baseline differences in sIgG and sIgG₄ to *D.pt.*, too (data not shown).

Compliance

Eighteen patients (8 a, 10 p) reported completely regular intake of sublingual medication over the whole year. Seven patients (four a, three p) reported minor irregularities with a maximum of 11 doses (7.5% of total amount) not being taken. Two patients (one a, one p) administered excessive amounts of the preparation at the beginning of the study (touching the dropper nipple onto the mucosa and pressing 7 times instead of letting 7 drops fall). They applied approximately a 1.5-fold higher

dose until the mistake was corrected after the first three months of therapy. One patient (p) interrupted his therapy for 6 weeks because of two vaccinations and prolonged it by that time in the end. Two patients (a) had their doses reduced because of side effects (see below).

Tolerance of therapy

One 14_{1/2} year old patient with asthma receiving active treatment dropped out after 8 weeks of therapy. He had no problems during the 3-week induction phase but reported a local swelling under the tongue and a subjective feeling of weakness after having reached the maintenance dose. He felt exhausted even after short walks, and he missed several weeks of school despite intensive treatment with inhalative steroids, theophylline and β -sympathomimetics and reduction of IT to 3 $\times$ 3 drops/week. Peak flow values remained normal as did three of four body-plethysmographic lung function tests. However, on one occasion a severe bronchial obstruction was registered. The general reaction was classified as a side effect although it was questionable whether it was attributable to the therapy. Finally the patient, his mother and the investigators, agreed to stop the treatment.

Local swelling, reddening, and tingling of the tongue, buccal mucosa and/or gingiva within less than 30 minutes of application were reported by five patients on active treatment and by one patient on placebo treatment. In one patient on active treatment the dose was reduced to 3 $\times$ 3 drops/week for 4 weeks and then gradually increased to 3 $\times$ 7 drops/week again over the next 4 weeks without any further local side effects.

Subjective assessment of clinical efficacy

Eleven patients on active treatment and nine on placebo assessed their health with a better score after 12 months. This improvement was significant in both groups (active treatment $p < 0.01$, placebo $p < 0.05$). There was no significant difference between active treatment and placebo group. The physician's

Table 2. House dust mite exposure throughout the study in active and placebo group. The table shows median (min-max) values in $\mu\text{g/g}$ dust

	0 months		3 months		12 months	
	Active	Placebo	Active	Placebo	Active	Placebo
Der p 1 - carpet	0.07 (0-5.3)	0.06 (0-37.8)	0 (0-9.54)	0.04 (0-22.1)	0.04 (0-6.18)	0.07 (0-39.3)
Der p 1 - mattress	0.09 (0-13.9)	0.10 (0-17.9)	0.06 (0-24.3)	0.06 (0-27.1)	0.04 (0-13.0)	0.11 (0-5.59)
Der f 1 - carpet	0.09 (0-37.3)	0.56 (0-12.43)	0.07 (0.04-41.4)	0.68 (0-4.02)	0.21 (0.07-3.05)	1.52 (0-28.8)
Der f 1 - mattress	0.94 (0-205)	1.43 (0-183.5)	0.33 (0-6.32)	2.4 (0-48.3)	0.26 (0.06-25.3)	5.84 (0-48.9)

Table 3. Efficacy of active and placebo treatment

	Active		Placebo		Effect comparison
	0 months	12 months	0 months	12 months	
IgE D.pt. (kU/l)	39.1 (3.5 - >100)	78.9 (20.4 - >100) **	33.3 (2.7 - >100)	47.4 (1.8 - >100) **	active > placebo #
Skin prick test - HEP 1 (SBU/ml)	2082 (< 500 - 10 875)	3469 (< 500 - > 13 500)	2187 (< 500 - > 13 500)	4228 (602 - >13 500)	n.s. effect difference
Nasal symptoms (mean score/d)	1.4 (0.25-3.4)	0.84 (0-3.9)	0.48 (0-3.1)	0.34 (0-1.4)	n.s. effect difference
Nasal symptom relief medication (n/all patients)		3 (12)		1 (10)	n.s. difference
Nasal provocation - PC ₄₀ Flow (SBU/l)	1 240 (110 - > 8 000)	1 380 (420 - > 8 000)	470 (70-1 180)	1 790 (275-6 500) **	active < placebo #
Pulmonary symptoms (mean score/d)	0.36 (0.04-1.3)	0.07 (0-1.00) *	0.07 (0-1.4)	0.28 (0-1.9)	active < placebo #
Pulmonary symptom relief medication (n/all patients)		5 (12)		8 (10)	n.s. difference
Bronchial provocation - PC ₂₀ FEV 1 Histamine (mg/ml)	0.7 (0.16 - > 8.0)	0.52 (0.05 - > 8.0)	1.7 (0.36 - > 8.0)	1.5 (0.61 - > 8.0)	n.s. effect difference

The table shows median (min-max) values for every variable except medication. Data for IgE and SPT refer to all patients, data for nasal effects refer to patients with rhinitis, data for pulmonary effects to asthmatics.

Nasal symptom relief medication: Antihistamines, nasal steroids; pulmonary symptom relief medication: β -Sympathomimetics, Theophylline prn.

Levels of significance for within-group differences: *: $p < 0.05$, **: $p < 0.01$. Level of significance for between-groups differences: #: $p < 0.05$.

assessment suggests a non significant higher prevalence of improvements in the treatment group (11/15), but also a considerable placebo effect (7/15 improved).

Objective assessment of clinical efficacy

Analyzing results within each group (a,p) we found a significant increase of specific IgE against *D.pt.* in both groups at 3 and 12 months, a reduction of pulmonary symptoms after 12 months in asthmatic patients on active treatment ($n = 11$), and an increase of PC₄₀ for nasal provocation after 12 months in the subgroup of rhinitis patients ($n = 10$) in the placebo group (Table 3). Total IgE increased significantly ($p < 0.01$) in both groups, sIgE *D.f.* increased in the active group ($p < 0.01$) and sIgG4 dropped in the placebo group ($p < 0.05$, data not shown). Total sIgG did not change significantly in either group (data not shown).

To compare the effects of therapy in both groups we calculated the differences of the values at 12 months and 0 months. In the active treatment group specific IgE against *D.pt.* and *D.f.* were increased significantly more than in the placebo group after 3 and 12 months. Asthma patients on active treatment recorded a greater reduction of pulmonary symptoms than placebo-treated asthmatics. Placebo treated rhinitis patients improved significantly more in nasal sensitivity than actively treated patients with rhinitis. There were no significant differences between all other therapy effects shown in Table 3 as well as for total sIgG and sIgG4 against *D.pt.* (data not shown).

Power analysis

The differences that would have been detected with 80% probability by our study design are summa-

rized in Table 4 for those parameters actually not showing differences between active treatment and placebo effects. For example effects on nasal symptoms would have been detected at a mean effect difference of 1.53 score points/day (theoretical range: -9 to +9 points/day, *de facto* range: -2.84 to +1.19 points/day).

Discussion

Two recent studies of oral (4) and sublingual (5) IT with house dust mite extracts in annual doses of about 5 times the amount usually given by injection have demonstrated clinical improvement after 24 months (4) respectively, 18 months (5), decreased nasal and bronchial sensitivity (5), increased specific IgG- and decreased specific IgE-levels in serum (4,5) after 12 months, decreased skin prick test reactions after 18 months (5), and decreased conjunctival sensitivity (4) after three years of therapy in HDM-allergic children with asthma and/or rhinitis. In our ongoing study with a similar dose we found a tendency for subjective improvement both in the view of the patients and the physician. However, we were unable to confirm the objective findings after 12 months except an improvement of pulmonary symptoms in the subgroup of asthmatic patients. In contrast to the cited studies specific IgE-levels in our active treatment patients were elevated after 3 and 12 months.

The reduction of pulmonary symptoms in asthmatics was the only objective benefit in actively treated patients. There was no improvement in bronchial reactivity or skin sensitivity in this group. In addition, the effects on pulmonary symptoms in asthmatics and nasal sensitivity in patients with rhinitis are contradictory. It is not plausible to assume that systemic immunotherapy has a positive

Table 4. Calculation of detectable differences between active and placebo effects for those variables not showing significant differences between active and placebo in this study ($\alpha < 0.05$, power 80 %). Data for skin test and bronchial provocation are expressed as differences in 3-fold resp. 2-fold concentration steps

	Number of patients (a/p)	Range of effects	Detectable effect difference
IgG D.pt. (%)	14 ^a /15	-1.14 to +6.20	2.89
IgG4 D.pt. (%)	14 ^a /15	-6.64 to +3.38	2.84
SPT dose equivalent to histamine 1 mg/ml (log 3 SBU/ml)	13 ^b /15	-1.81 to +2.74	2.04
Nasal symptoms (mean score/d)	11 ^a /10	-2.84 to +1.19	1.53
Bronchial provocation - PC20FEV 1 Histamine (log 2 mg/ml)	10 ^c /10	-2.50 to +2.20	1.87

^aone dropout; ^bone dropout, one patient not evaluated because wheal to histamine 0.1 % > wheal to histamine 1 % at 0 months; ^cone dropout, one patient without provocation because of severe bronchial obstruction at 0 and 12 months.

effect in asthmatics and a negative effect in patients with rhinitis. Regarding the relatively high pulmonary symptom score in actively treated asthmatics and the relatively low nasal sensitivity threshold in rhinitis patients on placebo at study entry (see Table 3), it is more reasonable to suppose that these non-significant baseline differences favoured the observed differences after 12 months in the two subgroups.

We examined whether our negative results after 12 months might have been the consequence of a lack of study power. Although the degree and frequency of symptoms in our patients at study entry was only moderate, a clinically relevant change of nasal symptoms would have been possible and detectable. The study would also have been powerful enough to detect relatively small effects on specific IgG. Effects on bronchial sensitivity would have been detectable at a minimum difference of 1.87 concentration steps between active treatment and placebo (theoretical range: 9 steps). Effects on skin prick test sensitivity would have been detected at a difference of 2.04 concentration steps (theoretical range: 4 steps). Concerning the QSPT, the study may have less power because of a relatively limited range in the concentrations of the test solutions (500 SBU/ml to 13 500 SBU/ml). Even though changes in skin sensitivity may not have been detected due to lack of study power, the consistency of negative results for the majority of clinical and immunological parameters argues against an existing but not detected desirable effect after one year.

Two significant differences between active and placebo group were undesirable: a greater frequency of minor local side effects and a greater increase of allergen specific IgE in the verum group. These differences on the other hand clearly demonstrate that sublingual immunotherapy did affect the immune system of our allergic patients and was not merely another version of placebo therapy.

These minor side effects were well tolerated by all but one patient. More than half of the verum patients did not experience any undesirable effects. Therefore we conclude that sublingual immunotherapy in the fivefold dose of subcutaneous therapy is well tolerated. This is consistent with the results of others (4, 5). Whether the symptoms of our dropout patient were caused by the study drug remains elusive.

In other studies some positive effects like decreased sensitivity in skin testing (5) or conjunctival provocation (4) were observed later than after 12 months of therapy. In contrast to our study both effects were observable in these studies already at 12 months although not being statistically significant at that time.

In ragweed allergic adults with rhinitis the dose response relationship in oral IT was examined (11). An allergen dose equivalent to subcutaneous therapy did not effect changes, but with oral doses 30 and 100 times higher clinical improvement and a rise in specific IgG antibody levels was achieved. Unfortunately this data is only published in abstract form at the present time. Correspondingly, a well documented study with birch pollen (12, 13) found a decrease in conjunctival sensitivity and a rise in IgG with doses 200 times the doses of injection therapy. Both authors reported only minor side effects.

Our doses may have been too low to be effective. On the other hand they have already been strong enough to induce minor side effects in nearly half of the patients. Much stronger doses could elicit much stronger side effects. Oral IT with a cat allergen dose 44 times that of injection therapy was accompanied by severe systemic reactions in two patients strongly suggestive to be induced by the allergen (14). High dose studies in children may be desirable. They should be practised with close surveillance of patients, perhaps similar to that in injection therapy, at least in the induction phase.

After one year of sublingual IT with a house dust mite extract dosed five times higher than that of subcutaneous therapy we did not find consistent clinical and immunological improvements in actively treated patients compared to placebo. There were no severe side effects. There is some evidence from studies in adults that suggest that higher doses may be more effective. Such therapies should be evaluated in children, with careful attention to possible stronger side effects.

References

1. MALLING H-J, WEEKE B. Position paper. Immunotherapy. *Allergy* 1993; 48 (SUPPL 14): 9-35.
2. CANONICA GW, BAGNASCO M, PASSALACQUA G, MOTTA C, BARTOLOMEI M, MARIANI G. Kinetics of radiolabelled allergen administered by sublingual and oral route (Abstract). *J Allergy Clin Immunol* 1996; 97: 230.
3. MØLLER C, DREBORG S, LANNER A, BJØRKSTEN B. Oral immunotherapy of children with rhinoconjunctivitis due to birch pollen allergy. *Allergy* 1986; 41: 271-9.
4. GIOVANE AL, BARDARE M, PASSALACQUA G, et al. A three year double-blind placebo-controlled study with specific oral immunotherapy to *Dermatophagoides*: evidence of safety and efficacy in pediatric patients. *Clin Exp Allergy* 1994; 24: 53-9.
5. TARI MG, MANCINO M, MONTI G. Efficacy of sublingual immunotherapy in patients with rhinitis and asthma due to house dust mite. A double-blind study. *Allergol et Immunopathol* 1990; 18: 277-84.
6. INTERNATIONAL CONSENSUS REPORT ON DIAGNOSIS AND MANAGEMENT OF ASTHMA. National Heart, Lung, Blood Institute, National Institutes of Health, Bethesda, Maryland 20892, Publication No.92-3091, MARCH 1992: 1.
7. VAN METRE JR TE, FRANKLIN ADKINSON JR N, KAGEY-SOBOTKA A, MARSH DG, NORMAN P, ROSENBERG GL. How should we use skin testing to quantify IgE sensitivity? *J Allergy Clin Immunol* 1990; 86: 583-6.
8. ZACH M. (Österreichische Gesellschaft Für Lungenerkrankungen Und Tuberkulose, Arbeitsgemeinschaft für Atemphysiologie). Empfehlungen Zur Standardisierung Der inhalativen Provokation zur Messung der Unspezifischen bronchialen Reaktivität. *Prax Klin Pneumol* 1986; 40: 356-64.
9. PUTTONEN E, MAASCH HJ. Measurement of blocking antibodies to pollen antigens by radiolabelled protein A from *Staphylococcus aureus*. *Int Arch Allergy Appl Immunol* 1981; 64: 157-66.
10. COHEN J. Statistical power analysis for the behavioral sciences 2nd edn. Hillsdale, New Jersey: Lawrence Erlbaum Associates 1988: 36.
11. CRETICOS PS, NACLEIRO RM, ADKINSON NF, NORMAN PS. Efficacy, safety and kinetics of oral ragweed immunotherapy in the treatment of allergic seasonal rhinitis (Abstract). *J Allergy Clin Immunol* 1990; 85: 165.
12. TAUDORF E, LAURSEN LC, LANNER Å, et al. Oral immunotherapy in birch pollen hay fever. *J Allergy Clin Immunol* 1987; 80: 153-61.
13. TAUDORF E, LAURSEN LC, LANNER Å, et al. Specific IgE, IgG and IgA antibody response to oral immunotherapy in birch pollinosis. *J Allergy Clin Immunol* 1989; 83: 589-94.
14. OPPENHEIMER J, ARESON JG, NELSON HS. Safety and efficacy of oral immunotherapy with standardized cat extract. *J Allergy Clin Immunol* 1994; 93: 61-7.