

Side-effects of allergen-specific immunotherapy. A prospective multi-centre study

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Summary

Background and objective The safety of allergen-specific immunotherapy (SIT) is a parameter of great interest in the overall assessment of the treatment. A clinical database was developed in order to obtain early warnings of changes in the frequency and severity of side-effects and sufficient data for the evaluation of possible risk factors.

Methods During a 3-year period, four allergy centres in Copenhagen, Denmark, included data from all patients initiating SIT to a common database. Information on initial allergic symptoms, allergens used for treatment, treatment regimens and systemic side-effects (SSEs) during the build-up phase was collected.

Results A total of 1038 patients received treatment with 1709 allergens (timothy, birch, mugwort, house dust mite (HDM), cat, and wasp and bee venom), 23 047 injections in total. Most SIT patients completed the up dosing phase without side-effects, but there was a significant difference between allergens: wasp (89%), birch (82%), HDM (81%), cat (74%) and grass (70%) ($P=0.004$). A total of 582 SSEs were registered in 341 patients. Most side-effects were mild grade 2 reactions (78%). A difference in severity between allergens was observed ($P=0.02$), with grass giving most problems. The type of allergen but not patient- or centre-related parameters seemed predictive of side-effects.

Conclusions Allergen extracts differ in their tendency to produce side-effects. Multi-centre studies like the present one allow more patients to be evaluated, and thereby provide a more efficient surveillance of side-effects. Online Internet-based registration to a central national database of every allergen injection would be an even more powerful tool for evaluation of risk factors and surveillance of side-effects.

Keywords asthma, clinical database, immunotherapy, rhinitis, side-effects

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Introduction

Side-effects in allergen-specific immunotherapy (SIT) are a central issue in the validation of the cost-benefit of the treatment. Most data on side-effects derive from smaller controlled studies and the incidence of systemic reactions in patients receiving SIT varies between such studies. Many factors are likely to contribute to these differences, for instance, the allergen applied [1, 2], the potency/formulation of the extract [3], the up dosing regime and top dose [4, 5], the severity and type of disease prior to treatment [6], premedication [7, 8] and difference in practical performance of the treatment [9]. To achieve reliable data on the prevalence, character and severity of

side-effects as well as the influence of patient and treatment parameters on these data, large-scale studies are needed. A large and long-term international multi-centre study has previously been performed on venom SIT [4]. Recently, a multi-centre study from Spain has been published including inhalant allergens. The number of side-effects was, however, small and more large studies are needed for evaluation of risk factors for side-effects to SIT [10].

There is an increasing demand from national authorities that every treatment should be evidence based with an ongoing validation of the quality of treatment. More regional and national clinical databases are subsequently being established. In the year 2000, an increase in severe

side-effects of SIT was suspected in Denmark, but no firm confirmation or explanation could be found because of incomplete data collection. In Copenhagen, a clinical database covering side-effects from SIT was therefore initiated. The idea was to obtain a description of the side-effects with sufficient data to allow identification of possible risk factors for systemic reactions. We further desired a tool for early warnings of changes in frequency of side-effects.

Material and methods

Design

Four allergy centres in Copenhagen, Denmark, performing immunotherapy accepted to establish a clinical database with a 3-years prospective registration of every new patient on SIT. A reporting form had to be filled in when treatment with an allergen was started, including the following: identification of the centre and age and gender of the patient, the indication for treatment (allergic rhinoconjunctivitis, allergic asthma, allergic reaction to hymenoptera) and the principles of the treatment (allergen, up dosing regime, premedication). Another reporting form was filled in when the patient had reached maintenance dose, summarizing the number of injections given to reach maintenance dose. If more than one allergen was administered concomitantly and a side-effect occurred, each allergen was considered a causing agent when the total number of side-effects per allergen during the up dosing phase was calculated. When the patient stopped the treatment at the centre, the reason for stopping was noted and again the number of injections and side-effects were registered. A third reporting form had to be filled in if a systemic side-effect (SSE) occurred, specifying the allergen, the time interval from injection to occurrence of side-effect and describing the symptoms (rhinoconjunctivitis, asthma, itching, urticaria, angio-oedema, stridor, hypotension, unconsciousness), the treatment (antihistamines, β_2 -agonist, corticosteroids, adrenaline), whether the patient had to seek medical attention after leaving the centre, whether the patient was hospitalized and whether SIT was terminated because of the side-effect.

All forms were faxed or mailed to the person in charge of registering and data were entered in the same database.

Centres

Three hospital centres and one private clinic participated in this study. All centres claimed that they followed the European Academy of Allergy and Clinical Immunology (EAACI) guidelines for inclusion of patients for SIT, with a history of rhinitis and/or asthma because of the relevant inhalant allergen, or previously severe systemic reaction to hymenoptera sting. The patient should have a positive

skin test and/or specific IgE to the relevant allergen. Each centre used their own treatment protocols. Two centres used antihistamine premedication (centres 1 and 3). One centre (centre 3) used only one allergen per day (single allergen) during the up dosing period, two centres mainly used one and maximum two concomitant allergens, whereas the private clinic (centre 4) used up to four allergens concomitantly.

In general, the patients were transferred to their general practitioners when the maintenance dose was reached. The clinical database had aimed at, but did not succeed in obtaining data from the general practitioners.

Allergen-specific immunotherapy

The hospital centres used individual modified cluster regimens with accumulated injections on separate days, on a weekly basis: centre 1, 7 weeks and 14 injections; centre 2, 11 weeks and 12 injections; and centre 3, 8 weeks and 10 injections. The private clinic (centre 4) used weekly injections, 15 weeks and 15 injections.

The extracts for immunotherapy were in an aqueous solution with aluminium hydroxide (Alutard SQ, ALK-Abelló, Hørsholm, Denmark). The activity of the extracts was given in standardized quality units (SQ-U). The extracts used were – with the amount of major allergens per top dose in brackets – *Betula verrucosa* (SQ 108 silver birch, 12.3 μ g Bet v 1), *Phleum pratense* (SQ 225 timothy, 20.2 μ g Phl p 5), *Artemisia vulgaris* (SQ 312 mugwort), *Dermatophagoides pteronyssinus* (Dp) (SQ 503 house dust mite (HDM), 9.8 μ g Der p 1), *Dermatophagoides farinae* (Df) (SQ 504 HDM, 13.8 μ g Der f 1), dog hair (SQ 553, 8.0 μ g Can d 1), cat hair (SQ 555, 14.6 μ g Fel d 1), *Apis mellifera* (SQ 801 bee venom, 100 μ g) and *Vespula* spp. (SQ 802 wasp venom, 100 μ g).

Patients

A total of 1038 patients (516 females and 522 males) received SIT with 1709 allergens. A subgroup of 625

Table 1. Number of treatment courses started with various allergens, classified as either concomitant i.e. administered together with other allergens on the same day, or single if given alone

Allergen	Concomitant (%)	Single (%)
Birch	468 (27.4)	181 (10.6)
Timothy	609 (35.6)	269 (15.7)
Mugwort	78 (4.6)	12 (0.7)
Dog hair	55 (3.2)	6 (0.4)
Cat hair	138 (8.1)	43 (2.5)
<i>Dermatophagoides pteronyssinus</i>	226 (13.2)	69 (4.0)
<i>Dermatophagoides farinae</i>	20 (1.2)	5 (0.3)
Bee venom	11 (0.6)	6 (0.4)
Wasp venom	104 (6.1)	95 (5.6)
Total	1709 (100)	686 (40.1)

patients (306 females and 319 males) was treated with a single allergen per day (686 allergens) (see Table 1). The mean age of the total group was 35 years (range: 7–84 years). For the subgroup, the mean age was 37.7 years (range: 8–84 years). The total number of allergens started in patients was distributed in four groups: 40% of the allergens were administered as single allergen and 30% as two, 21% as three and 9% as four concomitant allergens on the same day, respectively. The frequency of the various allergens is reported in Table 1. The indication for immunotherapy was asthma (4.5%), asthma and rhinoconjunctivitis (32%), rhinoconjunctivitis (57%) and hymenoptera sting reactions (6.5%).

Statistics

Cross-tabulations of categorical variables were analysed by the χ^2 test. Group comparison of continuous variables was carried out by the Mann–Whitney *U*-test (or Kruskal–Wallis test if more than two groups were present). Sex, asthma, centre and allergen extract were tested as possible risk factors for side-effects during the up dosing phase, by binary logistic regression. Statistical analyses were performed in SPSS 12.0 for Windows.

Results

At the end of the 3-year registration period, 763 patients had reached the maintenance dose with 1250 allergens. In the subgroup treated with a single allergen per day, 455 patients had reached maintenance dose with 494 allergens. Forty-one patients (4%) with 50 allergens stopped treatment because of complications (systemic reactions, local reactions, worsening of allergy symptoms): birch (6), *Dp* (10), cat (10) and grass pollen (24). These numbers correspond to 1% of the treatments started with birch, and 4%, 4%, 7% of treatments with grass pollen, *Dp* and cat, respectively.

Of the patients reaching the maintenance dose with one or more allergens, 77% reached the maintenance dose without side-effects if treated with one allergen per day as opposed to 71% if treated with more than one allergen per day ($P = 0.046$). The combinations of allergens were not considered.

A total of 23 047 injections were registered, with 21 027 injections (91%) representing the number of injections given until the maintenance dose was reached. The corresponding number was 7268 injections (32%) in the subgroup of patients with a single allergen treatment per day.

The significance of the different allergens on the occurrence of side-effects is blurred when more than one allergen is injected the same day. It was therefore decided to present data from single allergen treatment separately, with 494 treatment courses reaching the maintenance

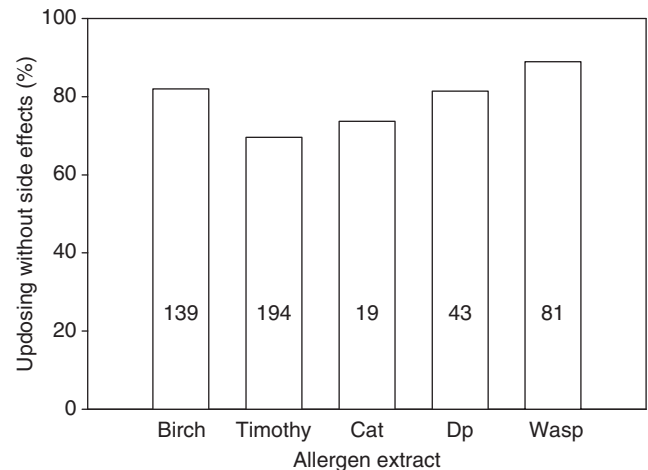


Fig. 1. Percentage of treatment courses with one single allergen per day reaching the maintenance dose without side-effects. Total number of treatment courses reaching the maintenance dose in columns. $P = 0.004$.

Table 2. Possible risk factors for having systemic side-effects during the dose increase phase (binary logistic regression analysis) in patients reaching the maintenance dose with or without side-effects

Variable	Significance	OR	95% CI for OR
Gender (female/male)	0.090	1.41	0.95–2.08
Indication (–/+ asthma)	0.293	0.80	0.52–1.22
Centre (reference is centre 4)	0.480		
Centre 1	0.439	0.81	0.46–1.40
Centre 2	0.387	1.45	0.62–3.37
Centre 3	0.378	0.81	0.50–1.30
Allergen (reference is wasp)	0.001		
Birch	0.234	1.62	0.73–3.57
Timothy	0.001	3.61	1.73–7.53
Cat hair	0.006	4.08	1.50–11.12
<i>Dermatophagoides pteronyssinus</i>	0.029	2.78	1.11–7.00

CI, confidence interval; OR, estimated odds ratio.

dose. Data from mugwort, dog hair, *D. farinae* and bee venom treatments were excluded from statistical analysis because of small numbers, 22 in total. There was a significant difference when treatment with the different allergens was compared (Fig. 1). Treatment with wasp venom had the highest proportion of treatment courses, reaching the maintenance dose without side-effects, and timothy SIT was the lowest. Logistic regression showed that only the type of allergen and not parameters such as sex, asthma and centre was predictive for side-effects during the up dosing phase (Table 2).

The side-effects were registered prospectively for all allergens started, but the number of injections was, as mentioned, not registered prospectively (up to a 6-month delay). It was therefore not possible to calculate the instant frequency of side-effects per injection during the study period. The number of side-effects in percentage of injections given was registered when the patient reached

the maintenance dose or if the patient stopped treatment at the centre. The frequency differed from allergen to allergen, with wasp venom (0.8%), birch (2.0%), grass (4.1%), *Dp* (5.9%) and cat (7.5%) ($P < 0.001$).

A total of 341 patients (33%) experienced SSEs: 66% had only one side-effect, 17% had two, 11% had three, 3% had four, 1% had five and 2% had seven to 17 side-effects. A total of 582 side-effects were reported, with 319 (55%) involving a single allergen, 29% with two, 14% with three and 2% with four concomitant allergens injected the same day.

Systemic reactions were graded according to the EAACI Position Paper from 1993, with inclusion of grade 2–4 reactions, with two indicating mild systemic reactions (rhinitis, mild asthma symptoms or $< 20\%$ reduction in peak expiratory flow (PEF), responding adequately to antihistamines or β_2 -agonist spray, respectively), three indicating non-life-threatening systemic reactions (urticaria, angio-oedema or severe asthma with a reduction of 20% or more in PEF, responding well to treatment), and four indicating anaphylactic shock (rapidly evoked reaction of itching, flushing, erythema, bronchial obstruction, etc., requiring intensive treatment) [11]. The side-effects were mostly mild grade 2 reactions (78%), with 20% grade 3 and 1% grade 4 reactions. A total of eight grade 4 reactions were observed, with timothy involved in all reactions (four as single allergen, one with concomitant mugwort, one with concomitant birch and mugwort, one with concomitant birch and *Dp* and one with concomitant birch, *Dp* and cat). All grade 4 side-effects were treated at the centres: seven were treated with adrenaline, and two were admitted to hospital for further observation.

Rescue medicine was administered in 78% of the side-effect cases, mostly with oral antihistamine or eye drops alone (61%). Adrenaline was used for treatment in 2% of the side-effects (in six cases as injection and five as inhalation); intravenous antihistamine was used in 4%, corticosteroid in 9%, β_2 -agonist inhalation in 23% and oral antihistamine in 62% of the side-effects.

The patients were observed at the centres for 30 min. A substantial part of the side-effects (50%) occurred after the patient had left the centre (Table 3). All grade 4 reactions occurred when the patient was still at the centre. Fifty-four percent of the grade 3 reactions occurred after the patient had left the centre. In 72% of these, late (> 30 min) grade 3 side-effects, urticaria was the reason for grading the side-effect as 3. The severity of urticaria was not evaluated. Almost all of the late side-effects were handled by the patient, only in 7% of the late side-effects did the patient return to the centre or emergency unit for treatment.

When looking at the severity of side-effects in the subgroup with a single allergen injection per day, differences were observed between allergens. The side-effects of birch immunotherapy were in general mild grade 2 reac-

Table 3. Cumulated frequency (%) of systemic side-effects occurring at different time intervals, for side-effects grades 2, 3 and 4, and for total side-effects

Side-effects	- 30 min	- 60 min	- 2 h	- 6 h	- 12 h	- 24 h	> 24 h
Grade 2	50.7	61.8	71.8	77.1	93.8	99.6	100
Grade 3	46.5	64.0	78.9	90.2	95.7	97.5	100
Grade 4	100						
Total	50.5	62.8	73.6	87.9	94.2	99.1	100

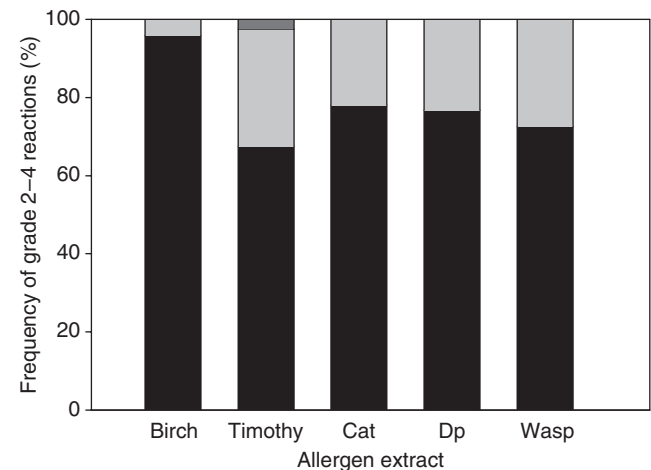


Fig. 2. Distribution of side-effects after allergen injections with one allergen per day, according to severity. Grade 2, dark grey; grade 3, light grey; grade 4, medium grey. $P = 0.02$.

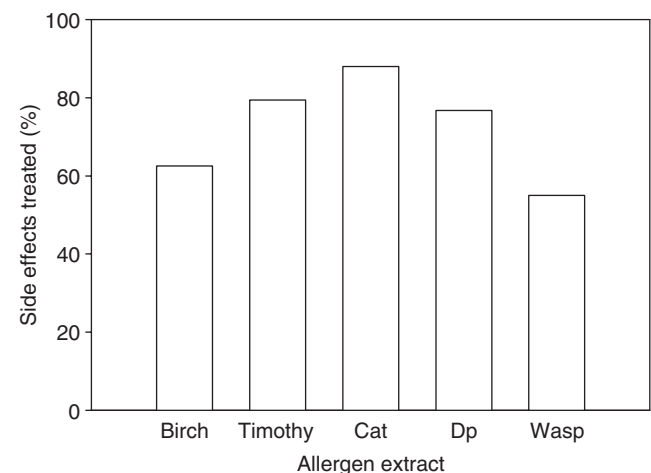


Fig. 3. Percentage of side-effects to each allergen given pharmacological treatment. $P = 0.01$.

tions, whereas timothy was the only allergen with severe grade 4 reactions after injection (Fig. 2). A significant difference in the need for treatment of side-effects was observed (Fig. 3). There was a difference in the profile of symptoms: SSEs of immunotherapy with all inhalant allergens included rhinoconjunctivitis at the same

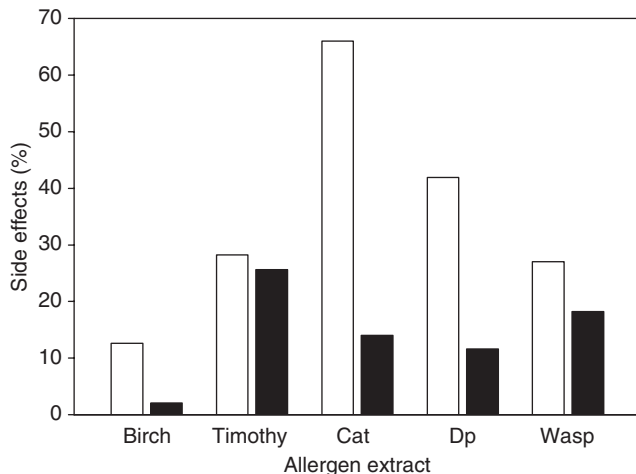


Fig. 4. Percentage of side-effects to each allergen presenting with asthma: white column. Urticaria: black column. For asthma, $P < 0.001$ and for urticaria, $P = 0.003$.

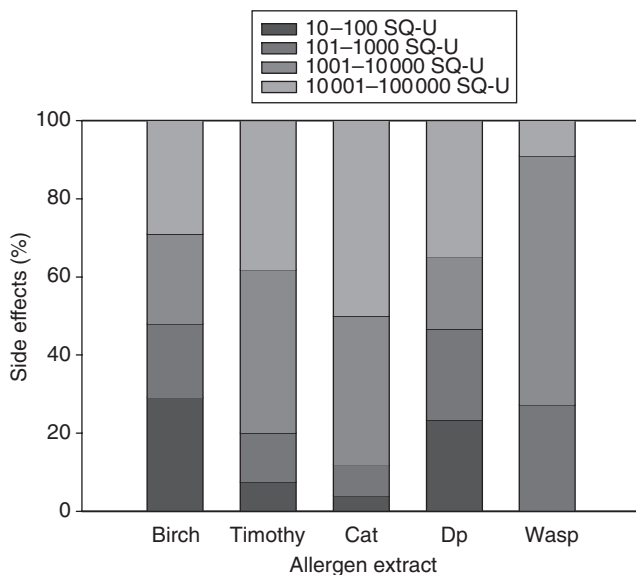


Fig. 5. Distribution of side-effects according to allergen dose.

magnitude, around 61% of reactions. The side-effects after cat and *Dp* immunotherapy presented a high frequency of asthma, with a significant difference between allergens ($P < 0.001$) (Fig. 4). The side-effects with timothy immunotherapy had a high frequency of urticaria (22%), with a significant difference between allergens ($P = 0.003$) (Fig. 4). There was a significant difference between allergens in the frequency of side-effects occurring early (< 30 min) and late (> 30 min), $P = 0.001$. The side-effects after SIT with birch included 47.8% early reactions, timothy (45.1%), cat (79.6%), *Dp* (55%) and wasp (18.2%). The difference between allergens disappeared if the definition of early and late reactions were increased to up to 2 h and later than 2 h, respectively.

Side-effects during the up dosing phase occurred at all dose levels (Fig. 5), with no significant pattern, except for grass pollen SIT. If side-effects occurred in this group at a dose of up to 10 000 SQ-U, only 26% were grade 3 (no grade 4), whereas 41% of side-effects induced by a higher dose were grades 3–4 ($P = 0.01$).

Discussion

National recommendations for practical performance of SIT differ and reflect the lack of sufficient data on the relative importance of various parameters on side-effects to SIT. When analysing the data for the subgroup treated with only one allergen per day, we found that the type of allergen was the only important parameter for side-effects. One could suspect the difference between allergens partly to reflect the severity of patient disease. One study showed that the pulmonary function of asthmatics was predictive of asthma during SIT with HDM [6]. Another study found that asthma patients less frequently reached the maintenance dose and more frequently had grade 2–4 reactions compared with grade 1 reactions [1]. The last study did not, however, perform multivariate analyses taking into consideration the different allergens. A third large-scale study found a higher ratio of systemic reactions among asthmatics and dust mite-allergic patients, but when logistic regression was performed asthma was not a risk factor [10]. In our study, we did not find asthma to be a risk factor either.

We found that wasp venom followed by birch SIT had the highest frequency of patients reaching the maintenance dose without side-effects and the lowest frequency of side-effects. Grass had the lowest frequency of patients reaching the maintenance dose without side-effects followed by cat and *Dp*. If we looked at the number of side-effects per injection to the maintenance dose, the number was higher with cat and *Dp* compared with grass. These results are in accordance with another study, only with minor differences, which could be because of small numbers of side-effects [1]. In this single-centre retrospective study, applying the same allergen extracts as we did, wasp and birch again showed the highest proportion of patients reaching the maintenance dose without side-effects, followed by grass, mite and cat [1]. In another study of allergic rhinitis patients, a higher number and more severe side-effects with grass SIT compared with birch SIT were observed [2]. The most obvious explanation for the difference between allergens would be a difference in strength of the extracts. The birch extract contains 12.3 μg major allergen Bet v 1 per 100 000 SQ-U compared with 20.2 μg major allergen Phl p 5 per 100 000 SQ-U in the grass extract. The nature of the allergen itself, and different number and proportion of major and minor allergens in the extract may also be a part of the explanation. The difference in potency could

also be a part of the explanation for the lower number of side-effects seen in other studies [3, 10, 12]. The difference between allergens could also reflect the heterogeneity between patients in terms of the range and strength of antibodies that they have against components of the extracts.

Even though in general we found no centre-related differences in side-effects, the centres differed in the practical performance of SIT in more than one possible important parameter (updosing regimen, antihistamine premedication, number of allergens, etc.). Previous studies have suggested that premedication with antihistamines reduces side-effects [7, 8]. One of the parameters considered to be a risk factor has been multiple injections a day. In our study, it seemed that patients with one allergen per day more often reached the maintenance dose without side-effects compared with patients with more than one allergen per day. But the result should be interpreted with caution, as the two patient groups are likely to be different. Almost all the patients who received more than one allergen per day came from one of the centres. Furthermore, the influence of the types of allergens was not accounted for in the statistical analysis.

Gender and age have also been considered as risk factors of side-effects. Divergent but mostly negative results have been presented [2, 4, 10–12]. Similarly, we did not find female/male sex to be a risk factor.

There seems to be a different profile of side-effects related to each allergen. Even though urticaria was observed with all allergens, our study and a previous study showed a difference in occurrence. Almost no side-effects with urticaria were observed in birch SIT whereas side-effects of grass SIT frequently gave rise to urticaria [2]. The reason for this is unclear. Also, asthma was observed with all allergens, but with a significantly higher frequency in SIT with cat and *Dp*. One could argue that asthmatics more often receive SIT with cat and mite. In our study, there was a tendency towards a higher frequency of patients with asthma \pm rhinitis in the cat and mite group, compared with the birch and grass group, but it did not reach statistical significance (data not shown). We did not register the severity of asthma, and the cat and mite group might have had a more severe asthma disease than the pollen group, which might explain the differences in frequency of side-effects with asthma. When we looked at the group with side-effects, there was a significantly higher frequency of asthma symptoms in patients with previous asthma compared with patients with no asthma in their history ($P < 0.001$, data not shown), again indicating an influence of patient disease on the symptom profile of side-effects.

There was a difference in the severity of side-effects between allergens, with grass eliciting more severe grade 3–4 reactions, mainly because of urticaria, but also because of anaphylactic reactions. The reason for this is

not clear. A higher potency of the extract could be a part of the explanation.

There was a significant difference in early and late reactions between allergens, when early and late reactions were defined by a time interval of up to 30 min and later than 30 min after injection. This difference between allergens disappeared if the time interval was increased to 2 h. An explanation is not evident.

All severe grade 4 reactions occurred within the observation period of 30 min, but still a high proportion of grade 2–3 side-effects occurred after the patient had left the clinic. In this study, increasing the observation period to 1 h did not seem to change the proportion of side-effects occurring at the clinic significantly. The patient handled the majority of late side-effects, and consequently a high degree of patient education is essential when performing SIT.

The frequency of side-effects is a necessary parameter for surveillance of SIT and demands concurrent recording of all side-effects and number of injections given. We tried to limit the number of reporting to the database. This resulted in a delay in the registration of the number of injections. Thus, updated information on changes in the frequency of side-effects was not available during the study.

National clinical databases offer a possibility for surveillance of quality of treatments through prospective recording of chosen indicators. The experience with the Copenhagen immunotherapy database showed that registration of all injections is needed for a complete data collection. We suggest a future clinical SIT database that would be entirely electronic. All injections could be registered online in a common electronic immunotherapy journal, with instructions for the practical performance of immunotherapy and with prompt registration of reactions to the injection. These data should automatically be transferred to a common national database with a possibility of measuring outcomes against regional and national results.

In conclusion, our data indicated that the allergens for SIT even from the same manufacturer differ in safety profiles, with grass giving most problems, and that neither sex nor history of asthma influences the frequency of side-effects. Larger studies are needed for evaluation of the broad spectrum of possible risk factors. For future studies on side-effects with SIT, an online Internet-based electronic registration is proposed.

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