

The local and systemic side-effects of venom and inhaled-allergen subcutaneous immunotherapy

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Summary. *Background:* Although immunotherapy is effective in allergic rhinitis, conjunctivitis, asthma and stinging insect hypersensitivity, it carries a risk of anaphylactic reactions.

Methods: In a 4-year retrospective survey, we investigated 1257 adult patients who had received venom or inhaled-allergen subcutaneous immunotherapy. The dose-increase phase was performed as the 2-day rush protocol for venom immunotherapy and the 6-week protocol for inhaled-allergen immunotherapy.

Results: A total of 904 patients received venom immunotherapy and 353 patients inhaled-allergen immunotherapy. The prevalence of systemic reactions was 13.6%. The frequency of systemic reactions was higher during the maintenance phase than in the dose-increase phase (9.6% vs. 5.9%) and was highest in both phases of treatment with honeybee venom ($P < 0.001$). The majority of systemic reactions were mild. Five (0.4%) patients had reaction with a fall of blood pressure and were treated with adrenaline. There was no fatal outcome. The systemic side-effects during the dose-increase phase of venom immunotherapy occurred at a median dose of 46 µg (range 2–100 µg). Large local reactions occurred in 13.9% of patients without any significant difference between the allergens.

Conclusions: We have shown that systemic reactions are not rare even during maintenance phase in patients with a well tolerated dose-increase phase of treatment. The most prominent risk factor for systemic reactions was immunotherapy with honeybee extract.

Key words: Side effects, venom, inhalation allergen, immunotherapy.

Introduction

Immunotherapy is effective in allergic rhinitis, allergic conjunctivitis, allergic asthma and stinging insect hypersensitivity [1–3]. Inhaled-allergen immunotherapy (IAIT) is indicated as a supplement to allergen avoidance and pharmacotherapy in patients with allergic rhinitis, allergic conjunctivitis and allergic asthma. Venom immunotherapy (VIT) is indicated in patients

with a history of IgE-mediated severe systemic allergic reactions including respiratory or/and cardiovascular symptoms [4]. The major risk with immunotherapy is the possible development of anaphylactic reactions to the allergen that is used for the treatment. Most severe reactions develop within 30 min after the injection, but reactions can also occur after this time.

Local allergic reactions associated with subcutaneous immunotherapy (SCIT) are fairly common and are not predictive for subsequent systemic reaction (SR) [5, 6], the more dangerous type of reaction because of the possibility of life-threatening anaphylaxis. Particular attention should be paid to patients with higher risk of severe SR, such as patients with asthma, especially if their asthma is unstable and they are taking β -adrenergic blocking agents [7, 8], which may make an immunotherapy-related SR more difficult to treat and delay the recovery. Nevertheless, immunotherapy is indicated in patients with life-threatening hypersensitivity to stinging insects and who also require β -blocker medication, because the risk of life-threatening reaction is greater after an insect sting in an untreated patient than after an immunotherapy-related SR [9].

The aim of our study was to retrospectively assess the frequency and types of side-effect in patients treated with SCIT (VIT and IAIT) and assess their influence on the course of SCIT.

Materials and methods

In this retrospective cross-sectional survey we investigated adult patients receiving VIT or IAIT in our clinic between January 2004 and December 2007. All patients received SCIT under the allergologist's supervision in hospital or in a hospital outpatient department. Patients' data were retrieved from the hospital information system (BIRPIS) and patients' charts; these were filled out at each visit and contained records of side-effects. Patients who had started treatment before 2004 were checked for side-effects in the maintenance phase only; if they had side-effects during that phase, the dose-increase phase was also checked. Patients with unstable asthma or patients taking β -adrenergic blocking agents did not receive immunotherapy.

Aqueous venom extracts (HAL Allergy BV, Haarlem, The Netherlands; Stallergens, Antony, France) and modified aeroallergens (allergoids) for pollen and house dust mite allergy (HAL Allergy BV) were used in the treatments. The dose-increase phase was performed as a 2-day rush protocol for VIT with a cumulative dose of 111 µg and a 6-week once-weekly injection

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for IAIT according to the producer's instructions. Patients were pre-treated with antihistamines during the induction phase of VIT. The maintenance doses were 100 µg of venom extract and 5 µg of allergoid extracts. In patients with SRs during VIT, we attempted to increase the maintenance dose to 200 µg.

A large local reaction (LR) was defined as a local swelling > 10 cm in diameter at the site of allergen injection and lasting > 1 day. SRs were classified according to the European Academy of Allergy and Clinical Immunology (EAACI) grading of severity for systemic side-effects:

- Grade I (mild): Localized urticaria, rhinitis or mild asthma (peak flow < 20% decrease from baseline)
- Grade II (moderate): Slow onset (> 15 min) of generalized urticaria and/or moderate asthma (peak flow 20–40% decrease from baseline)
- Grade III (severe, non-life-threatening): Rapid onset (< 15 min) of generalized urticaria, angioedema, or severe asthma (peak flow > 40% decrease from baseline)
- Grade IV (anaphylactic shock): Immediate reaction of itching, flushing, erythema, generalized urticaria, stridor (angioedema), immediate asthma, hypotension etc.

Statistical analysis

SPSS version 16.0 was used for data management and statistical analysis. Descriptive statistics were used and data are presented as numbers and percentages of cases. The chi-squared test was used to test for differences between groups.

Results

In a four-year period, 1257 patients (mean age 41 years, range 13–76; 40.9% female) received SCIT: 904 (72%) patients received either wasp VIT (521, 57.6%), bee VIT (359, 39.7%) or VIT with both venoms (24, 2.7%); 353 (28%) patients received IAIT with grass pollen (122, 35%), early tree pollen from birch, hazel in alder (55, 16%), birch pollen (15, 4%), house dust mite (54, 15%) or two or more allergens (107, 30%). A total of 523 patients (41.6%) started immunotherapy before 2004 and were checked only in maintenance phase; 734 patients (58.4%) started treatment after 2004 and were checked in both phases (dose-increase and maintenance).

Overall, 195 SRs were recognized in 171 (13.6%) patients: 74 occurred during the dose-increase phase and

121 during the maintenance phase (5.9% vs. 9.6% of all patients); 21 patients had SRs in both phases. VIT SRs occurred during the dose-increase phase at a median dose of 46 µg (range 2–100). There was no fatal outcome.

SRs occurred most frequently in bee-venom VIT (110 patients) and were more severe than SRs in wasp VIT or IAIT (Table 1). The majority of SRs were mild and treated with antihistamine and corticosteroids. A grade IV SR requiring adrenaline occurred in five (0.4%) patients, all receiving bee VIT; four of the SRs occurred in the maintenance phase. SRs during the maintenance phase occurred from the first month until month 16 and within 20 min after the injection. VIT was continued with a higher maintenance dose of honeybee-venom extract in all five patients.

Among 171 patients who had SRs, 44 (25.7%) prematurely stopped the treatment (22 honeybee VIT, 10 wasp VIT, 3 honey bee and wasp VIT, 9 IAIT): the physician stopped treatment in 15 patients (34%) because of SRs, 14 (32%) stopped at their own wish and 15 (34%) stopped without any known reason.

A total of 175 (13.9%) patients had LRs in either the dose-increase phase or the maintenance phase; 18 (1.4%) had LR in both phases. The incidence of LRs was comparable in all three allergens and in both phases, ranging from 3.9% to 12.7% (Table 1). In one patient receiving IAIT, subcutaneous nodules attributed to aluminum-adsorbed extracts appeared in the maintenance phase. Thirteen (7.4%) patients with LRs prematurely stopped treatment (2 honeybee VIT, 4 wasp VIT, 7 IAIT).

Discussion

Our retrospective study analyzed a large group of patients undergoing SCIT. We aimed to establish the incidence of LRs and SRs during treatment and the influence of these on the course of SCIT.

LRs associated with SCIT are fairly common, with frequency ranging from 26% to 86% of patients, rate per injection 0.7–4.0% [10, 11]. We found a low rate of LRs

Table 1. Allergic reactions during immunotherapy. The prevalence of local and systemic reactions and severity of systemic side-effects according to the EAACI Grading of Severity for Systemic Side Effects. The frequency of local reactions to different allergens was not statistically significant; the frequency and severity of systemic reactions was statistically significant (chi-squared test). The highest frequency and severity of systemic reactions were observed in both phases of treatment with extract of honeybee venom

	Dose-increase phase					Maintenance phase				
	Local reaction	Grade of systemic reaction (according to Mueller)				Local reaction	Grade of systemic reaction (according to Mueller)			
		I	II	III	IV		I	II	III	IV
Wasp	22 (4.0%)	10 (1.8%)	6 (1.1%)	1 (0.2%)	0	69 (12.7%)	11 (2.0%)	6 (1.1%)	5 (0.9%)	0
Honeybee	15 (3.9%)	11 (2.9%)	23 (6.0%)	5 (1.3%)	1 (0.3%)	37 (9.7%)	29 (7.6%)	30 (7.8%)	7 (1.8%)	4 (1.0%)
Aeroallergens	20 (5.7%)	12 (3.4%)	4 (1.1%)	1 (0.3%)	0	33 (9.4%)	20 (5.7%)	7 (2.0%)	2 (0.6%)	0
P value	0.427	0.320	0.000	0.054	/	0.199	0.000	0.000	0.226	/

(13.9%) in our patients. However, it is important to stress that LRs in patients treated with pollen allergoids were as common as in patients receiving VIT. We did not analyze the frequency of LRs in relation to the number of injections.

A retrospective study of 2206 patients undergoing IAIT reported SRs in 5.2% of the patients and 0.06% of the injections [12], and a retrospective study of both IAIT and VIT reported 0.4% SRs according to the number of injections [13]. In the literature, the per-patient incidence of SRs attributable to VIT reveals high variation ranging from 0 to 46% [4]. Such difference in reported SRs is partly due to the use of different VIT protocols and SR classification systems [4]. A prospective EAACI multicenter study analyzed side-effects and risk factors in 840 patients on VIT (71% with wasp-venom extract, 27% with honeybee-venom extract). The majority of VIT SRs were very mild, occurring in 19% of patients treated with wasp-venom extract and 24% of patients treated with honeybee-venom extract, and with a higher frequency during the dose-increase phase than the maintenance phase (1.9% vs. 0.5% of all injections). The risk factors were female sex, bee-venom extract and rapid dose increase [14]. The lower frequency of SRs (6.9% of patients) was seen in an ultrarush dose-increase schedule [15]. A Polish study observed SRs in 15.2% of patients during the 5-day rush induction phase of VIT, whereas severe adverse events were present in 5.9% patients. The risk factors were bee venom immunotherapy and female sex [16]. In a study in Spain it was concluded that immunotherapy is a safe treatment when EAACI guidelines are strictly followed [17].

Placebo-controlled studies with patients on IAIT in the treatment of asthma have reported adverse reactions in 29% of patients in the actively treated group vs. 10% of patients receiving placebo. The SRs included urticaria, worsening of asthma, facial edema and rhinoconjunctivitis [2]. Patients with allergic rhinitis undergoing IAIT had SRs in the range 3–15% [3].

The incidence of unconfirmed near fatal reactions (NFRs) after allergen immunotherapy in North America was 23 per year (5.4 events per million injections) in the period 1990–2001. Treatment during the height of the pollen season (46% of respondents) and dosing errors (25% of respondents) were cited as the two most important contributing factors in NFRs. Overall, 93% NFRs occurred in the clinics of board-certified allergists who were present during the reaction; the remaining 7% NFRs occurred in primary care settings [18]. Of the 17 fatalities, 15 (all on IAIT) had asthma, and in nine patients asthma was considered the susceptibility factor that contributed to the fatal outcome. Ten (59%) fatal events occurred in clinics of board-certified allergists who were present during the reaction; seven (41%) fatal events occurred outside the clinics (5 in primary care settings and 2 during home administration) [19].

In accordance with the EAACI multicenter study, we found a lower frequency of SRs in wasp VIT and a higher grade of SRs in honeybee VIT. We also observed a higher frequency of SRs during the maintenance phase than in the dose-increase phase. All grade IV reactions

occurred in honeybee VIT. There is no clear reason why side-effects are more frequent with honeybee sensitization treatment than with wasp treatment. However, the quality of the extracts may be the cause, and honeybee-venom should be more highly purified, with a lower concentration of non-allergenic proteins [4, 14, 20].

VIT SRs occurred during the dose-increase phase at a median dose of 46 µg (range 2–100 µg), which is comparable to the EAACI study where the median dose in the dose-increase phase was 30 µg (range 0.01–150 µg), and the Polish study where the majority of SRs in the dose-increase phase developed at a dose of 40 µg or 60 µg of the venom extract [14, 16].

Our study has some limitations: it was retrospective, and the results reflect the quality of documentation of side-effects in routine clinical practice.

In spite of the effectiveness of SCIT, the major risk is the possible development of systemic anaphylactic reactions. We have shown that SRs are not rare even during maintenance phase in patients with a well tolerated dose-increase phase of treatment. The entire SCIT procedure should be administered only by healthcare professionals trained in the recognition and treatment of anaphylaxis and following EAACI guidelines.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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