

Original article

Side-effects of insect venom immunotherapy: results from an EAACI multicenter study

Background: The effect of venom immunotherapy (VIT) is well documented, but fear of systemic side-effects (SE) may prevent its use. The study aimed to analyze the character and frequency of SE and risk factors.

Methods: In a prospective study, 19 European centers included patients starting on VIT for systemic reactions to insect stings. Various dose regimens were applied.

Results: Data from 840 patients with a total of 26 601 injections were obtained. Seventy-one percent were treated with *Vespula*-venom extract and 27% with honeybee-venom extract. Twenty percent of patients had SE corresponding to 1.9% of injections during dose increase and 0.5% during the maintenance phase. The vast majority of the 280 reactions were mild: only one-third required medical treatment. Injected or inhaled adrenaline was applied in six patients, of whom only one had a drop in blood pressure and collapse. Female sex, bee-venom extract, and rapid dose increase, but not severity of insect sting reactions, increased the risk of SE. The severity of SE was less in males but was not related to age, treatment phase, species of insect, or severity of insect sting reactions.

Conclusions: The frequency of SE was low, and the majority of these could be managed without treatment. Risk was increased in females, in bee-venom-treated patients, and in those with rapid dose increase.

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Side-effects have been crucial when discussing the pros and cons of allergen-specific immunotherapy. In some countries, the fear of side-effects has led to strict regulations preventing a more widespread use of this treatment (1, 2).

One could expect the patient's type of allergy and severity of symptoms to influence the frequency, severity, and kind of side-effects with subsequent immunotherapy. Since insect-venom-allergic patients after being stung present with a variety of severe reactions in several organs, a fear in patients and physicians of more severe and frequent side-effects with venom immunotherapy (VIT) than with, for instance, pollen immunotherapy, is not uncommon. However, in an early study, this fear turned out to be groundless (3).

In the USA, a large-scale study of insect allergy was performed just after the introduction of venom extracts in the 1970s (3). In Europe, at present, reliable and comparable large-scale information on the prevalence, character, and severity of side-effects to VIT is scarce and not available from either pharmaceutical companies or national authorities. The aim of the present study was to collect data prospect-

Table 1. Classification of abnormal sting reactions and side-effects. Modified from Mueller (4)

Type of reaction	Symptoms
0) Large local	Swelling > 10 cm for >2 days
1) Minor	Itching, urticaria, edema, malaise, anxiety
2) General	Chest tightness, palpitations, dizziness, nausea, abdominal pain
3) Severe	Somnolence, respiratory difficulties, vomiting, diarrhea, incontinence
4) Anaphylactic	Confusion, drop in blood pressure, feeling of impending doom, unconsciousness, cyanosis, death

ively in order to be able to assess the types and frequencies of side-effects with VIT with different extracts, dose regimens, and patient groups.

Material and methods

Design

All allergy centers represented by the Subcommittee on Insect Allergy of the European Academy of Allergology and Clinical Immunology (EAACI) were invited to join the study. In participating centers, patients with systemic reactions starting on VIT were included prospectively. For each patient, a form was filled in describing symptoms, atopy, and results of diagnostic testing. A reporting form had to be filled in if a side-effect occurred, and at regular intervals, lists of the number of injections given to each patient were updated. Insect sting reactions and side-effects during VIT were reported and subsequently graded according to a scale (Table 1) (4). The inclusion period was 1 year except in a few centers with a large intake of patients, where the number of patients had to be limited to avoid dominance. The subsequent study period was 2 years.

In several centers, patients were referred to their own general practitioners for further VIT after a certain number of injections. To ensure standardized reporting of data, only injections given in the participating centers before referral were included in the study.

Centers

Twenty-three centers intended to participate in the study. Four did not include patients; subsequently, data from 19 centers in 10 European countries could be evaluated.

Patients

A total of 840 patients (457 males and 383 females) were included. The mean age was 41 years (range: 5–77 years) in the total group and in the major subgroup treated with extract from one insect species only. All patients had experienced at least one systemic reaction to an insect sting, and none had received VIT previously. Basic clinical data are listed in Table 2. All patients had either a positive skin test or specific IgE to the relevant allergen.

VIT

No effort was made to harmonize the treatment regimen in the different centers, and, although the number of venom extracts was limited, most centers used their own treatment protocols. Updosing was performed either by weekly injections, by rush regimens with several injections on a few consecutive days, or by clustered regimens with accumulated injections on separate days, often with weekly intervals. No attempt was made to compare data from patients receiving different rush regimens.

The majority, 417 males and 365 females, were treated with one venom extract. Fifty-eight patients had two venom-extract treatments concomitantly (Table 3). Commercial extracts with venom from wasp (*Vespula* species), honeybee, and paper wasp (*Polistes* species) were applied. The number of patients treated in various centers differed considerably (Table 4). Extracts were in an aqueous solution either with or without aluminum hydroxide added to give a depot effect. Some patients switched from one type of extract to another, the majority switching to the depot version when the maintenance dose was reached, and a few switching due to repeated side-effects with one type of extract.

Table 2. Clinical data at inclusion

	One-allergen group	Total group
Sex		
F	47%	46%
M	53%	54%
Age – years (mean, range)	41 (5–77)	41 (5–77)
Unrelated allergy		
Asthma	5%	5%
Rhinitis	13%	12%
Urticaria	5%	5%
Interval (years) after sting (mean, range)	2 (0–26)	2 (0–26)
Severity of sting reaction		
Mueller class 1	12%	12%
Mueller class 2	24%	23%
Mueller class 3	41%	41%
Mueller class 4	23%	24%
Positive skin test		
Wasp	83%	84%
Honeybee	46%	47%
Specific IgE for		
Wasp	82%	83%
Honeybee	52%	53%

Table 3. Allergen extracts and dose-increase regimen for 840 patients included and 782 treated with venom extract from only one insect species. Some patients changed from depot to nondepot, or vice versa

	No. of treatment series	
	One-allergen group	Total group
Extract		
Depot	122	174
Nondepot	656	720
Not specified	4	4
Venom		
<i>Vespula</i> species	557	615
Honeybee	212	256
<i>Polistes</i> species	13	27
Updosing regimen		
Weekly	113	179
Clustered	63	97
Rush/ultrarush	508	524
Mixed	98	98

Statistics

Cross-tabulations of categorical variables were analyzed by the chi-square test. Group comparison of continuous variables was done by the Mann-Whitney U-test (or the Kruskal-Wallis test if more than two groups), and correlation was expressed by the nonparametric Pearson correlation coefficient. Stepwise logistic regression was applied to determine the influence of the various parameters on the occurrence of side-effects in the individual patients. A level of probability above 5% was regarded as significant. Statistical analyses were done by SPSS 7.0 for Windows®.

Table 4. Number of patients treated with various allergens in participating centers (patients treated with venom extract from only one insect species)

	IT allergen			Total
	Honeybee	<i>Vespula</i>	<i>Polistes</i>	
Centre				
1	8	41		49
2	13	16		29
3	2	35		37
4	19	44	4	67
5	2	3		5
6	3	9	1	13
7	2	5	2	9
8	4	4		8
9	15	18		33
10		61		61
11	4	19		23
12	4	33		37
13	31	10		41
14	10	61	2	73
15	1	2		3
16	50	122		172
17	29	37		66
18	13	16	4	33
19	2	21		23
Total	212	557	13	782

Table 5. Treatment of side-effects to VIT in patients treated with venom extract from only one insect species

Type of treatment	% of reactions
No treatment	66
Oral treatment (total)	18
Antihistamine	17
Corticosteroid	6
Injection (total)	19
Adrenaline	3
Antihistamine	15
Corticosteroid	11
Inhalation (total)	6
Adrenaline spray	3
Inhaled β -agonist	2

Results

A total of 26 601 injections were given, 23 602 to patients receiving treatment with only one extract. In this subgroup, 12 122 injections were given during the dose-increase phase (mean: 15 per patient, SD: 5) and 11 480 during the maintenance phase (mean: 15 per patient, SD: 16).

Ninety-two percent of the patients received a maintenance dose of 100 μ g, 3% left the study before reaching a maintenance level, 2% had to stay on a lower level (20–90 μ g), and 3% received 110–200 μ g at each injection during the maintenance phase.

A total of 299 systemic side-effects were reported; of these, 280 occurred in patients treated with one venom only. In this subgroup (and in the total group), 20% of the patients had at least one systemic reaction and 1.2% of injections elicited reactions. Side-effects occurred during dose increase at a median dose of 30 μ g (range:

Table 6. Systemic side-effects to VIT (patients treated with venom extract from only one insect species). Calculations are based on frequency of side-effects in individual patients

Type of patient/treatment	Occurrence of systemic side-effects (mean and range)		
	Percentage of injections during updosing	Percentage of injections during maintenance	Percentage of patients
Sex			
F	2.0 (0.0–52)*	0.9 (0.0–100)	25*
M	1.2 (0.0–63)*	1.2 (0.0–100)	15*
Extract			
Depot	1.2 (0.0–21)	0.2 (0.0–14)	17
Nondepot	1.6 (0.0–63)	1.3 (0.0–100)	20
Venom			
<i>Vespula</i> species	1.5 (0.0–63)	0.6 (0.0–100)*	19
Honeybee	1.8 (0.0–52)	2.4 (0.0–100)*	24
<i>Polistes</i> species	0 (0.0–0.0)	0 (0.0–0.0)	0
Updosing regimen			
Weekly	0.8 (0.0–21)*	0.2 (0.0–14)	12*
Clustered	1.3 (0.0–9.1)*	0.1 (0.0–3.8)	22*
Rush/ultrarush	2.1 (0.0–63)*	1.5 (0.0–100)	24*
Mixed	0.5 (0.0–9.1)*	1.0 (0.0–67)	8*
Total group	1.6 (0.0–63)	1.1 (0.0–100)	20

* $P < 0.05$.

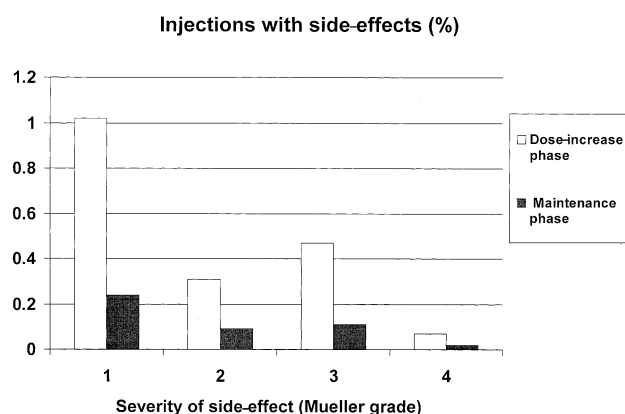


Figure 1. Side-effects during dose increase and maintenance phases classified according to severity.

0.01–150 µg) and during the maintenance-phase at a median dose of 100 µg (range: 30–150 µg). The detailed analyses below were made in the subgroup treated with one venom only.

The majority of systemic symptoms were very mild (Fig. 1), and only one-third required treatment. Oral antihistamine was the drug most frequently applied (Table 5). A drop in blood pressure was reported in nine cases, but only one patient received adrenaline. This patient and one other patient suffered fainting/collapse. In the latter case, no adrenaline was administered.

The frequency of reactions was higher during the dose-increase phase than the maintenance phase (mean: 1.9% vs 0.5% of all injections). When analyzed separately, female sex, rapid dose-increase regimens, and treatment with bee-venom extract seemed to increase the risk of side-effects (Table 6). If analyzed in a model taking the correlation between the different parameters into account, only female sex and rapid dose-increase (rush) regimens turned out to be risk factors for systemic side-effects. In addition, patients with pre-existing allergic rhinitis more often had side-effects (29% vs 19%, $P < 0.05$). The following parameters

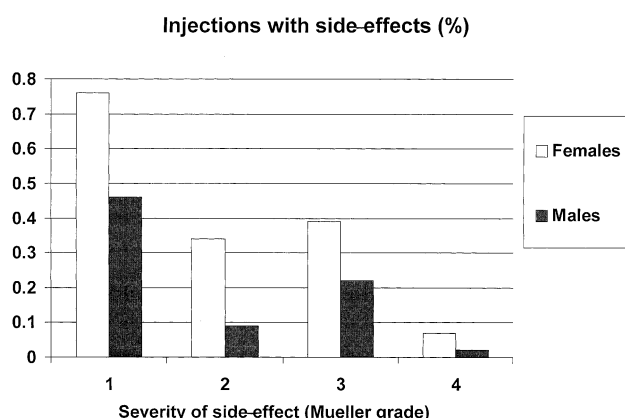


Figure 2. Side-effects in women and men classified according to severity.

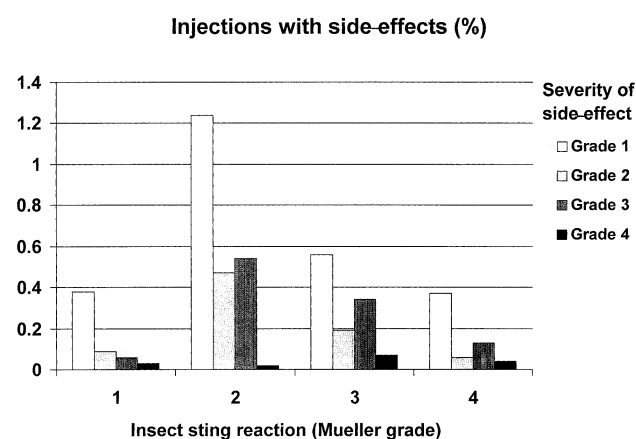


Figure 3. Severity of last reaction to relevant insect for different severity of side-effects.

did not influence the risk of systemic side-effects in either separate analyses or logistic regression: age, pre-existing asthma or urticaria, severity of original insect sting symptoms, time interval between sting and symptoms, number of systemic sting reactions, progression in sting reactions, type of extract (with or without aluminum hydroxide), and number of venom extracts used for treatment (one or two).

When side-effects occurred, they were less severe in males (Fig. 2). Severity was not related to pre-existing asthma, rhinitis, or urticaria; severity of original insect sting reaction (Fig. 3); whether or not the patient had had a positive skin test or allergen-specific IgE for the relevant venom pretreatment; type of extract; or the insect venom used for treatment.

Side-effects occurring during the dose-increase phase did not differ from side-effects during the maintenance phase with respect to severity (Fig. 1), interval after injection, or duration, but reactions during the maintenance phase were treated more often (52%) than reactions during up dosing (31%). Reactions occurred in patients not differing with respect to age or severity of the original insect sting reaction.

Rapid onset of side-effects correlated positively to short duration of these reactions ($R = 0.47$, $P < 0.001$). Severity was not correlated to age of patient, time interval from original insect sting to symptoms, or time interval from injection to occurrence of side-effects.

Discussion

The present multicenter study has made it possible to collect a very large set of data covering a variety of treatment regimens administered to a high number of patients with different symptoms. This has enabled analyses not possible in local settings.

We intended to make the reporting forms as self-explanatory as possible and collected data on a running basis in order to correct misunderstandings and make

the data as uniform and complete as possible. The basic information describing patients at inclusion was obtained in a standardized form. The reporting of side-effects was less standardized, as some centers registered every slight symptom/sensation in a detailed fashion, whereas other using the same extract and dose regimen reported fewer but more substantial side-effects. Subsequently, reporting of Mueller class I side-effects was probably somewhat less reliable than the reporting of more severe reactions. However, the main conclusion of the study that severe side-effects to VIT are very infrequent was not invalidated by the methodological problems mentioned. An analysis including only objective symptoms would have reduced the frequency considerably, but could not be done retrospectively.

The fact that only one-third of the systemic reactions were treated illustrates the low severity of the reactions. Adrenaline was applied in only one of the nine cases in which a drop in blood pressure was reported. Blood pressure levels were not registered in this study, but the limited need for this effective and appropriate treatment must reflect limited changes in blood pressure, since all centers could be regarded as experienced in VIT and the treatment of side-effects.

The finding that rush up dosing seems to imply a higher risk of side-effects is not unexpected (5). A slower and less "aggressive" regimen would have a less drastic impact on the immune system and thereby also be less likely to induce side-effects. However, in one comparative study with VIT, the same frequency per injection (and a lower frequency per patient) was observed (6). A very low frequency of systemic side-effects (7% of patients) was seen in an extremely rapid dose-increase schedule (ultrarush) (7). In fact, such regimens were applied in some patients in a few of the participating centers, but since no attempt was made to standardize or obtain very detailed information on the many dose regimens applied in this study, only broad conclusions could be drawn. The number of injections needed to reach the maintenance dose did not differ between the dose-regimen groups. This indicates that only a minority of patients were offered the ultrarush regimen. Additional investigations are needed if, for instance, subtypes of rush regimens are to be compared.

The present study confirms the finding that there seem to be more side-effects with bee-venom than wasp-venom treatment (7–11). The reason is unknown. No differences were found in side-effects in patients starting treatment with aqueous and with aluminum hydroxide-precipitated venom extracts. A few patients switched during up dosing due to side-effects, and others switched after reaching the maintenance dose to be able to increase the dosing interval. Since the background for the switch was not registered systematically, a detailed analysis comparing the two types of extract was not possible.

As in a recent British study (10), female patients had more side-effects than male and these tended to be more severe than the reactions registered in the male group. This finding might be explained by a lower threshold among women for reporting symptoms.

In other studies, the frequency of side-effects with VIT has varied between 0% and 100% in different patient groups exposed to different extracts and different dose regimens (3, 5, 10, 12). In the present study, about one-fifth of the patients had one or more systemic side-effects. This figure may seem high, but several aspects have to be taken into account. Firstly, the little need for medical treatment of the side-effects confirms that these were generally very mild. Secondly, a reaction rate of below 2% during dose increase and 0.5% at the maintenance dose is generally lower than side-effects reported for other allergens administered for less serious diseases (13). In addition, adrenaline self-injection, the alternative to VIT, seems inconvenient to many patients, and the efficacy of adrenaline treatment is not 100% (14); therefore, VIT is to be preferred in spite of the side-effects.

In several centers, maintenance treatment was continued by general practitioners. The lower risk of side-effects after up dosing confirms that this is a sensible way to organize treatment if specialist resources are limited or are far away from the patient. This lower risk during maintenance treatment has been a general finding (3, 10). However, since reduction accounts only for the frequency, and not the severity, of side-effects during this phase, general practitioners, as well as specialists, should be ready to treat anaphylactic reactions. In the present study, we intended to collect data from general practice if patients continued treatment there. Unfortunately, the information was not sufficiently extensive to allow analysis. However, there is no reason to expect a higher frequency of side-effects in general practice, since many of the patients continuing treatment in hospital were in fact "problem patients" selected because of previous side-effects.

Selection of candidates for VIT by sting challenge, as was done in one of the participating centers, can exclude more than half of the patients with otherwise positive diagnostic tests (15). One would expect the remaining patients to have an increased risk of side-effects. However, this could not be demonstrated in the present study, in which only a very small percentage of the patients had been challenged in hospital before treatment. Similarly, one would have expected previous severe insect sting reactions to indicate an increased sensitivity to the venom extract and, similarly, an increased risk and severity of side-effects. As in another large-scale study (8), we could not confirm this hypothesis. One explanation could be that the Mueller classification cannot categorize intermediate and severe reactions properly. Recently, a new side-

effect classification has been proposed (primarily for patients with inhalant allergy) (2), but this might imply a better prediction.

In conclusion, it has been possible to carry out a large and long-term multicenter study under the auspices of the Insect Venom Allergy Subcommittee of the EAACI. The results obtained should encourage others to carry out collaborative studies on different aspects of allergy. Our results showed that the

majority of systemic side-effects of VIT were very mild even though they occurred in one-fifth of the patients. Few predictive factors were identified. Rapid dose regimens gave rise to more side-effects than slow. However, ultrarush treatment was not investigated separately. The higher risk of side-effects in women remains unexplained. It seems safe to let a well-prepared general practitioner perform the treatment, at least during the maintenance phase.

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