

Original article

Safety of rush insect venom immunotherapy. The results of a retrospective study in 178 patients

Background: Venom immunotherapy (VIT) is regarded as an established and efficient treatment of Hymenoptera venom allergy. Different frequencies of side-effects have been reported in the literature, depending on the hyposensitization regimen (conventional outpatient programme, rush immunotherapy, ultra rush immunotherapy) and the venom preparation. Aim of this study was to evaluate safety and tolerance of rush VIT in patients treated with a 7-day protocol in our department.

Methods: VIT protocols of 178 patients treated at the Department of Dermatology and Allergy of the University of Bonn were analysed retrospectively. All patients had been treated with a standardized venom preparations (ALK-SQTM). We used a modified VIT-protocol with a 2-day break to reduce systemic side-effects.

Results: During the course of VIT in 15 patients (8.4%) systemic reactions grade I (Mueller scale) were observed, in seven (3.9%) grade II, in six (3.4%) grade III and in four (2.2%) grade IV. A total of 146 patients (82.1%) had no or only local reactions.

Conclusions: The rate of systemic adverse reactions Mueller Grade I–IV of 17.9% of the 'Bonn rush VIT protocol' appears to be relatively low compared with the data in the literature.

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About 0.8–5% of the total population of Europe and the US have a history of generalized skin or systemic reactions to insect stings (1). In Central Europe stinging insect anaphylaxis is most often caused by honeybees (*Apis mellifera*) and common wasps (*Vespa germanica* and *V. vulgaris*).

Less commonly bumblebees (*Bombus* spp.) and other wasps (*Dolichovespula* spp. and *Polistes* spp.), hornets (*Vespa crabro*), woodbees (*Xylocopa* spp), ants (Formicidae) midges or horseflies are involved (2).

Insect venom immunotherapy (VIT) is regarded as an effective prophylactic treatment. According to the literature protection from future severe reactions can be achieved in up to 90% of cases (3). Standards of VIT were defined by the 'International Committee of Insect Venom Allergy' published in this journal in 1993 (4).

Following identification of the causative insect, the severity of the reaction to the insect sting in the presence of specific IgE antibodies is used to determine indication for insect VIT. Cutaneous tests, like the intracutaneous serial endpoint titration are also part of the diagnostic work-up. In the absence of either specific IgEs or a convincing relevant medical history however, these tests should not lead to initiation of VIT on their own.

The profession of the patient particularly in high risk occupations (pastry-cooks, beekeepers and forestry worker) has to be taken into consideration.

Different regimens of insect venom hyposensitizations are in use, ranging from conventional outpatient programmes (several weeks), rush immunotherapy (5–7 days) to ultra rush immunotherapy (1–3 days). All these protocols are followed by maintenance applications required every 4–8 weeks (1, 3, 5–13).

Different rate of side-effects of VIT have been reported in the literature. Most systemic adverse reactions in rush VIT appear on the final days of immunotherapy at a dose of 50–100 µg per injection (1, 3, 5–13).

Comparison of incidence rates is difficult to achieve, due to the variety of methods employed in the documentation of adverse reactions.

Patients and methods

The VIT protocols of 178 patients (age: 10–76 years, mean: 40.18 years) treated in the Department of Dermatology and Allergy of the University of Bonn were analysed. All patients had been treated with venom preparations by ALK-Scherax (ALK-SQTM, ALK-Scherax GmbH, Hamburg, Germany). A total of 184

immunotherapy courses were included in the study: 149 patients were treated with wasp venom in one cycle, three patients with wasp venom in two cycles, 24 patients with bee venom and two patients with wasp and bee venom (one of the latter with bee venom in two separate cycles).

The field sting reaction leading to the referral to our department was classified using the classification proposed by Mueller (14)

Table 1. Classification of allergic reactions after insect bites by Hymenoptera [after H.L. Mueller, completed by U.R. Mueller, with modifications (14)]

Systemic reactions	
Grade I	Generalized urticaria, pruritus, nausea and anxiety
Grade II	Any symptom of I and two or more of the following: angio-oedema (grade II on its own), tightness, vomiting, diarrhoea, abdominal cramps and dizziness
Grade III	Any symptom of grades I and II and two or more of the following: dyspnoea, wheezing, stridor (all of which already grade III on their own) dysphagia, dysarthria, hoarseness, general weakness, numbness and fear of death
Grade IV	Any symptom of grades I–III and two or more of the following: drop of blood pressure, collapse, syncope, incontinence and cyanosis
Severe local reactions	Swelling at the site of injection with a diameter >10 cm (>24 h)
Unusual reactions	Serum sickness, generalized vasculitis, affection of renal, nervous or haematopoietic system

Table 2. The Bonn rush VIT protocol (100.000 SQ-E = 100 µg insect venom)

Day	Preparation	Concentration (µg/ml)	Volume (ml)	Dose (µg)
Day 1 (Monday)	Lyophilisate	0.000001	0.2	0.0000002
		0.00001	0.2	0.000002
		0.0001	0.2	0.00002
		0.001	0.2	0.0002
Day 2 (Tuesday)	Lyophilisate	0.01	0.2	0.002
		0.01	0.4	0.004
		0.01	0.8	0.008
		0.1	0.2	0.02
Day 3 (Wednesday)	Lyophilisate	0.1	0.4	0.04
		0.1	0.8	0.08
		1	0.2	0.2
		1	0.4	0.4
Day 4 (Thursday)	Lyophilisate	1	0.8	0.8
		10	0.2	2
		10	0.4	4
		10	0.8	8
Day 5 (Friday)	Lyophilisate	100	0.2	20
		100	0.3	30
		100	0.4	40
		100	0.5	50
Day 6 (Monday)	Lyophilisate	100	0.6	60
		100	0.7	70
		100	0.8	80
Day 7 (Tuesday)	Lyophilisate	100	0.9	90
	Depot	100	1	100
Total dose				555.55*

* Compared with a total dose of 438.46 µg in the original 7-day protocol by ALK-Scherax.

(Table 1). Allergen-specific IgE against wasp and bee venom were measured using the Pharmacia-Cap-System™ (Pharmacia Diagnostics, Uppsala, Sweden).

Inclusion criteria for VIT were a field sting reaction with a Mueller grade of ≥1 and concentration of specific IgE of ≥1 KU/l (CAP-FEIA™, Pharmacia Diagnostics).

Rush VIT was initiated on inpatients with four subcutaneous injections per day. Full emergency resuscitation facilities were available at all time. Therapy was started with an initial venom dose of 0.0000002 µg. Over the following 7 days the amount was then increased up to a dose of 100 µg. Most systemic adverse reactions in rush VIT appear on the final days of the immunotherapy programme at a dose of 50–100 µg per injection. Therefore we used a modified VIT protocol with a 2-day break after the fifth day at a reached dose of 50 µg. The total venom dose after 7 days was 555.55 µg compared with 438.46 µg in the original 7-day protocol by ALK-Scherax™ (ALK-Sherax GmbH; 'The Bonn rush VIT protocol', Table 2).

Local and systemic side-effects were measured and documented. Grading of observed systemic side-effects was performed using the Mueller score (Table 1).

Results

Field sting reactions

Field sting reactions grade I had occurred in 27 (15.2%) of the patients (two bees/25 wasps). Thirty-one patients (17.4%) had reactions grade II (four bees/27 wasps), 69 grade III (12 bees/56 wasps/one double sensitization) and 51 grade IV (six bees/44 wasps/one double sensitization).

Specific IgE

Mean value of bee-specific IgE, measured in bee venom allergic patients, was 34.78 kU/l (standard degression 35.98/median 14.65 kU/l). None of these patients had CAP class 0 (<0.35 kU/l), four had CAP classes I or II (0.35–3.5 kU/l), thirteen had CAP class III or IV (3.51–50 kU/l) and seven CAP class V or higher (>50 kU/l). Mean value of wasp-specific IgE in wasp venom sensitized patients was 15.549 (standard degression 20.318/median 9.16 kU/l). None of these patients had CAP class 0 (<0.35 kU/l), 32 had CAP classes I or II (0.35–3.5 kU/l), 106 had CAP classes III or IV (3.51–50 kU/l) and eight CAP class V or higher (>50 kU/l).

Adverse reactions

During the course of VIT in 15 patients (8.4%) systemic reactions grade I were observed, in seven (3.9%) grade II, in six (3.3%) grade III and in four (2.2%) grade IV. A total of 146 patients (82.2%) had no or only local reactions.

The day of onset of the maximum side-effect in bee VIT patients was day 6, in wasp VIT patients day 5 (Fig. 1). Local reactions were treated with ice packs and topical corticosteroids (0.1% betamethasone valerate). In 83 patients, systemic drug therapy was required. The

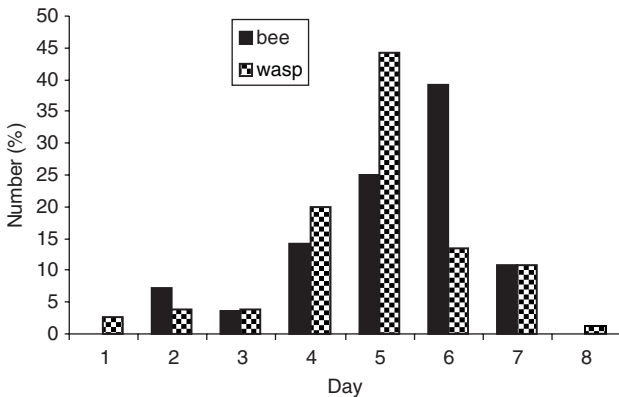


Figure 1. Day of onset of maximum severity symptoms in venom immunotherapy in our patient cohort.

medication used were antihistamines (ceterizine p.o., clemastine i.v.), corticosteroids (methylprednisolone i.v.), metoclopramide (p.o.) and 0.9% sodium chloride (i.v.). Additionally, systemic side-effects were managed by transient interruption of immunotherapy a restarting with a lower dose. In nearly all of these cases the programme could be continued and the aspired maximum dose was achieved. However, in nine patients (4.9%) side-effects led to a discontinuation of VIT. The reasons for discontinuation in these nine patients were: (i) hypertensive episodes, (ii) anaphylactic reactions with dyspnoea, coughing, dysphagia and hypertension, (iii) systemic reactions with dizziness and nausea, (iv) hypertension with headache and nausea, (v) hypotension, (vi) urticaria with larynx tightness, (vii) dizziness and hypotension, (viii) acute pharyngitis and (ix) generalized eczema.

Discussion

Insect VIT is an efficient and widely used therapy. However, comparison of data concerning side-effects in VIT is problematic, because an international standard classification of VIT adverse effects does not exist. Therefore, comparative data about the rate of side-effects depending on the protocol employed is sparse.

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Table 3. Systemic adverse effects (Mueller Grades I–IV): comparison of earlier studies with our results

Study	No. of patients (bee and wasp)	Percentage of systemic side-effects (Mueller I–IV)
Przybilla et al. 1987 (10)	290	38
Berchtold et al. 1992 (15)	26	27
Mueller et al. 1992 (3)	205	36
Laurent et al. 1997 (8)	97	45
Brehler et al. 2000 (1)	1317	22.4
Mosbech and Muller 2000 (9)	840	20
Wenzel 2003 (present study)	178	17.9

The rate of systemic side-effects as documented reliably in earlier studies ranges from 20 to 45% (1, 3, 8–10, 15). Compared with the literature data the safety of the ‘Bonn rush VIT protocol’, with a rate of systemic adverse reactions (Mueller Grades I–IV) of 17.9% appears to be relatively high (Table 3). In our cohort most systemic reactions during VIT appeared on days 5 and 6. On day 7, the day with the highest concentration of insect venom, we observed a comparatively small number of systemic reactions in our cohort (Fig. 1). This effect and our low number of systemic adverse reaction might be a result of the 2-day weekend break after day 5 included in the ‘Bonn rush VIT protocol’, which is not part of most of the other rush VIT protocols in use (4). An additional cause of the relatively small numbers of systemic side-effects is the high share of wasp venom patients in our cohort. However, there was no significant difference between side-effects of wasp and bee venom patients.

To allow comparison of side-effects of different regimes of VIT, like ultra rush VIT, rush VIT and conventional VIT, the use of a generally accepted classification would be helpful. The Mueller Score, designed for the classification of allergic reactions after field insect stings, has been used by some authors also to classify adverse reactions of VIT (8, 10, 11). We would therefore suggest to use an established classification like the Mueller Score to document systemic side-effects of this treatment in future studies.

In the context of quality assurance in future, safety and tolerance of this therapy should be evaluated regularly.

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