

Hymenoptera ultra-rush venom immunotherapy (210 min): a safety study and risk factors

J. Birnbaum, M. Ramadour, A. Magnan and D. Vervloet

UPRES EA 3287, Service de Pneumo-allergologie, Hôpital Sainte Marguerite, Marseille, France

Summary

Background In this study, which summarizes our last 5 years of experience, we evaluated the side-effects of ultra-rush venom immunotherapy and the possibility to define some risk factors for side-effects as age, Hymenoptera venom used for treatment, treatment phase, severity of prior insect sting reaction, concentration of skin test positivity, and level of specific IgE.

Methods In our protocol on day 1, an initial venom dose of 0.1 µg was followed by 1, 10, 20 µg at 30-min intervals and then 30 and 40 µg at 60-min intervals. Patients who completed this protocol received two booster injections of 50 µg on day 15 and one of 100 µg on day 45. Subsequently, monthly 100 µg boosters were given.

Results Fifty-one children (9.20 ± 3.41 years) and 207 adults (40.62 ± 14.00 years) underwent an ultra-rapid venom immunotherapy (ultra-RVIT). Single ultra-RVIT was administered to 195 patients: 69 with honeybee, 123 with yellow jacket and three with wasp venoms. Two venoms were injected into 59 patients: 42 with yellow jacket and wasp, 17 with yellow jacket and honeybee. Four patients received the three venoms.

The frequency of immediate systemic reactions (SR) was not significantly different between adults and children: 11.2% vs. 10.8%.

SR were experienced more frequently on day 1 ($n = 33$). They were uncommon on day 15 ($n = 2$) and on day 45 ($n = 1$). No late reactions have been observed. Honeybee venom induced significantly more SR (30%) vs. yellow jacket (3.2%) and wasp venom (6.1%). Among the 33 patients who experienced a SR on day 1, 24 had a reaction grade 1 or 2 and nine had a reaction grade 3 or 4. There is a significant risk for patients with a prior reaction grade 3 or 4 to experience a SR during venom immunotherapy (VIT).

The strength of positive skin tests and the level of specific IgE were not related to an increased risk of SR ($P = \text{NS}$).

Conclusion Treatment with honeybee extract induced more SR than the treatment with yellow jacket and wasp venom. Doses increase phase on day 1 is risk factors for SR of ultra-RVIT, as well as the severity of the prior reaction. Age, degree of positive skin tests, and specific IgE are not risk factors.

Keywords honeybee, insect venom allergy, risk factors, side-effects, wasp, yellow jacket

Submitted 5 June 2002; revised 20 September 2002; accepted 30 September 2002

Introduction

Venom immunotherapy (VIT) is an effective treatment for patients with a history of IgE-mediated allergic reactions to Hymenoptera stings [1]. Since the first immunotherapy with pure venom was carried out in 1974 [2, 3], protocols of various duration have been devised in an effort to maximize protection, minimize side-effects and optimize patient convenience. With a slow protocol the time required to reach the maintenance dose of 100 µg, generally considered as adequate [4], is several weeks [5–7], with a rush protocol is several days [8–11] and with an

ultra-rapid protocol is few hours [12–15]. The ultra-rapid venom immunotherapy (ultra-RVIT) has the obvious advantage of achieving rapid protection with minimum inconvenience for the patient. VIT aims to induce tolerance to Hymenoptera venom but can be complicated by systemic reaction (SR). Many different regimens for build up and for maintenance VIT have been used in the literature, making it difficult to compare the results. Studies using rush protocols have suggested that they are at least as safe as slower protocols [12–15]. In a previous study, we found that our ultra-RVIT protocol, which used a cumulative venom dose of 101.1 µg of venom over 3.5 h (210 min), resulted in fewer systemic reactions compared to 6-h and 4-day protocols, which attained cumulative doses of 226.6 µg and 527.6 µg, respectively [14].

However, SR are a significant problem, especially when honeybee venom (HBV) is used [16, 17]. It is thus far not possible to

Correspondence: J. Birnbaum, UPRES EA 3287, Service de Pneumo-allergologie, Hôpital Sainte Marguerite, 270 Bvd de Ste Marguerite, 13274 Marseille Cedex 09, France.

predict the SR that may occur with any VIT regimen, even with doses tolerated previously [18]. Attempts to define patient-related risk factors for SR have failed. Defining the risk factors might allow some adaptation of VIT regimens in these subjects in order to minimize the occurrence of dangerous SR. Since our 1992 initial report, we have routinely performed ultra-RVIT in a large number of patients, allowing a retrospective analysis on clinical data with (reactor) and without (non-reactors) SR to VIT in order to detect which patient profile is at risk for SR to VIT. Therefore, we summarize our last 5 years of experience with ultra-RVIT evaluating during this period the SR of ultra-RVIT, and the possibility to define some risk factors for SR: age, Hymenoptera venom used for treatment, treatment phase, severity of initial insect sting reaction, degree of skin test positivity, degree of specific IgE positivity. To date, any studies using the same regimen and a large group of patients (children and adults) have been looking for possible risk factors.

Materials and methods

Patients

We analysed the data of 258 Hymenoptera venom-allergic patients referred for VIT to our department between January 1994 and October 1999. Patients were selected to receive ultra-RVIT based on the criteria recommended by the European Academy of Allergy and Immunology Subcommittee on insect venom allergy [19]. VIT was recommended if there was a history of an immediate systemic reaction after a Hymenoptera sting and the demonstration of IgE-mediated allergy by skin tests and/or the presence of venom-specific IgE serum antibodies to the respective venom. Immediate systemic reactions were classified according to the system proposed by Mueller, from grade 1 to grade 4 [20].

Skin tests

In all patients, venom-specific IgE were demonstrated by skin tests with serial 10-fold dilutions of honeybee (HB), yellow jacket (YJ) and wasp (W) venom (Bayer Pharma, Hollister Stier Laboratories, Paris, France). Skin test reactivity was tested by performing intradermal tests on the forearm with increasing concentrations from 0.001 µg/mL to 1 µg/mL. Skin tests were considered positive if reactions (weal of at least 5 mm in diameter with erythema) occurred after 15 min at a concentration of 1 µg/mL or less [19]. The lowest concentration resulting in such a reaction was defined as the endpoint concentration.

Control tests were first performed to verify that skin reactivity was normal: 9% codeine phosphate was used as a positive control and diluent as the negative control.

Venom-specific IgE antibodies

In all patients, venom-specific IgE antibodies to HB, YJ and W venom were determined by a commercial available radio-immunologic assay (Pharmacia, Uppsala, Sweden). Results were expressed in kU/L and were negative below 0.35 kU/L.

Venom selected for ultra-RVIT

The venom was chosen with reference to the patient's history of entomological identification, skin test and/or sIgE results:

1. Description of the Hymenoptera, consistent skin tests and/or specific IgE assay: VIT performed with the venom of the species of Hymenoptera identified.
2. Inconclusive entomological identification, positive skin tests and/or specific IgE assay for HB and YJ stings: double immunotherapy.
3. Conclusive entomological identification, positive skin tests and/or specific IgE assay for all venoms tested: immunotherapy programme using only the venom of the insect identified by the patient.
4. Identification of wasp as the offending species but without further distinction between YJ and W, positive skin tests and/or specific IgE assay for YJ and W: double immunotherapy using the venoms of both species (particularly in Mediterranean areas).
5. For bumblebee or hornet stings, the absence of specific venom requires either no immunotherapy or else immunotherapy, respectively, with HB or YJ venom.

In all cases, the immunotherapy was carried out with one or more of the same venoms used for skin testing.

Ultra-RVIT

Ultra-RVIT is outlined in Table 1 and was monitored by the same physician at the Department of Chest Diseases and Allergy, in the day care unit in Marseille, France. The initial venom dose for ultra-RVIT was the same regardless of the patient's age and sensitivity. A cumulative venom dose of 101.1 µg divided into six subcutaneous injections was administered over 3.5 h on day 1: an initial venom dose of 0.1 µg was followed by 1, 10, and 20 µg at 30-min intervals, and then 30 and 40 µg at 60-min intervals. The patient was seen again after 2 weeks (day 15) and given 50 µg in each of two injections at an interval of 30 min, and subsequently returned after 1 month (day 45) for an injection of 100 µg. The venom injections on days 15 and 45 were given under the same medical supervision as on day 1 and thereafter at intervals of 4 weeks (100 µg, maintenance dose) on an outpatient basis. Only the patients who completed the ultra-RVIT (day 1) continued the protocol on days 15 and 45. All injections were applied subcutaneously to the outside of the upper arm, at least 10 cm above the elbow. In this protocol, indwelling intravenous lines were used in all cases on days 1, 15 and 45. Full emergency resuscitation equipment was readily available. In case of SR following a venom injection on day 1, the protocol was immediately stopped and the patient received intravenous injections of H1 antihistamines.

Table 1. Ultra-rapid venom immunotherapy (3.5 h)

	Time	Injected venom (µg)
Day 1	0 h	0.1
	30 min	1
	1 h	10
	1.5 min	20
	2.5 min	30
	3.5 min	40
Day 15	0 h	50
	30 min	50
Day 45	One injection of 100 µg	
Monthly	One injection of 100 µg	

and corticosteroids. The use of adrenaline was decided according to the severity of the SR. The patients were kept under observation until the next morning and then left hospital with an appointment for the following week. A new protocol has now been established based on repeated low venom doses each week to obtain a maintenance venom dose of 200 µg/mL over several weeks.

If two or three venoms were required, they were administered in separate protocols a few days apart.

Patients did not receive a pre-treatment with antihistamines. Thereby, the incidence of allergic side-effects during ultra-RVIT was artificially not reduced [21–23].

Clinical surveillance protocol

The condition of the skin, pulse rate, blood pressure and respiratory rate were recorded before and 30 min after each injection. Any objective adverse event attributed to the ultra-RVIT injections was noted. The threshold venom dose and the type of symptoms were recorded.

Statistical evaluation

The following parameters were considered for analysis: sex, age, Hymenoptera species involved in the prior systemic sting reaction, severity of the prior systemic reaction, degree of positive skin tests and positive venom-specific IgE and compared in the two groups of patients: reactors and non-reactors by a Chi-square method.

Logistic regression analysis was used to rate the effect of such covariates on risk of systemic reaction during the ultra-RVIT. The model included quantitative variables: sex, age, lower concentration of positive skin tests, level of venom-specific IgE, Hymenoptera species involved, grade of the prior sting reaction. We performed a backward step-wise analysis with a variable numbers of iterations, leading to an estimate of the odd ratio, together with its confidence interval and degree of significance. SPSS 6.1 for the Power Macintosh (SPSS, Chicago, IL, USA) was used as software.

Results

Prevalence of systemic reactions to immunotherapy with HB or YJ or W venom

Between January 1994 and October 1999, 258 patients (98 females, 160 males) ranging in age from 3 to 79 years underwent an ultra-RVIT: 51 children (9.20 ± 3.41 years; age ≤ 15 years, 3 months) and 207 adults (40.62 ± 14.00 years). Three hundred and twenty-five ultra-RVIT were performed. Single ultra-RVIT was administered to 195 patients: 69 patients with HB venom, 123 patients with YJ venom and three patients with W venom. Fifty-nine patients received ultra-RVIT with two different venoms: 42 with YJ and wasp, 17 with YJ and HB, and four patients with all three venoms (Table 2).

On day 1, 33 (12.79%) patients experienced a systemic reaction during the increase in doses. The time interval between injection and SR was below 30 min. On days 15 and 45, we observed two and one systemic reaction, respectively. No late reactions have been observed. HB venom induced significantly more systemic reactions (30%) than YJ (3.2%) and W venom (6.1%). SR were experienced more frequently on day 1 ($n = 33$).

They were exceptional on day 15 ($n = 2$) and on day 45 ($n = 1$). The frequency of immediate systemic reactions was not significantly different between adults and children (11.2% vs. 10.8%; Table 3).

Of the 36 patients with SR, only one interrupted VIT because of repetitive SR preventing the increasing venom doses.

Characteristics of systemic reactions

The SR during ultra-RVIT (day1) were mainly mild in 24 patients: 21 adults and three children, with cutaneous symptoms as localized urticaria and/or angio-oedema and/or erythema. Severe symptoms (grade 3 and 4) were observed in nine patients: six adults and three children. Two patients experienced an hypotension without collapse and loss of consciousness (Table 4). Severe cardiovascular symptoms were not observed in children (Table 5). SR were observed with undiluted venom (100 µg/mL) in 24 patients, between 10 and 40 µg. Eight patients had a SR at a venom concentration of 1 µg/mL and only one patient experience a SR at 0.1 µg (Fig. 1).

Clinical profile of patients with systemic reaction to ultra-RVIT

When we compared the severity of the SR during ultra-RVIT and prior to VIT (mild grade 1 and 2 reactions vs. severe grade 3 and 4 reactions), there was a significant correlation between the VIT SR and the unexpected SR as well as in adults ($P = 0.016$) as well as in children ($P = 0.025$). The patients who experienced a grade 3 or 4 reaction to VIT more frequently had a grade 3 or 4 reaction after the sting (Tables 4 and 5).

The degree of positive venom skin tests was not significantly different between the reactors and the non-reactors when we compare the group with the highest degree of positive skin test (0.001 µg) to the rest of the group. However, in the group of

Table 2. Venom type used for ultra-RVIT

	Honey bee	Yellow jacket	Wasp
Children ($n = 51$)	17	38	10
Adults ($n = 207$)	73	148	39
Total VIT treatment course ($n = 325$)	90	186	49

One venom ($n = 195$): 69HB, 123YJ, 3W; two venoms ($n = 59$): 17HB + YJ, 42YJ + W; three venoms ($n = 4$): HB + YJ + W.

Table 3. Incidence of systemic reactions (SR) during ultra-RVIT

	Day 1	Day 15	Day 45	% SR
Honeybee ($n = 90$)	25	1	1	30.0
a = 73	(a = 20)	(= c)	(= a)	28.8
c = 17	(c = 5)			35.3
Yellow jacket ($n = 186$)	5	1	0	3.2
a = 148	(a = 4)	(= a)		3.4
c = 38	(c = 1)			2.6
Wasp ($n = 49$)	3	0	0	6.1
a = 38	(= a)			7.6
c = 10				0
Total	33	2	1	11.1
260 adults (a)	27	1	1	11.2
65 children (c)	6	1		10.8

Table 4. Severity of systemic reaction vs. severity of prior sting reaction in adults

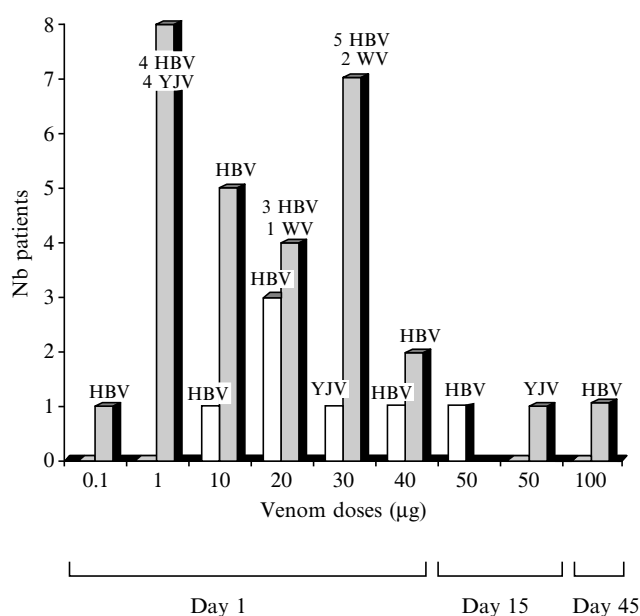
Side-effects of VIT Day 1 (Mueller grade)	Prior sting reaction			
	Grade 1	Grade 2	Grade 3	Grade 4
Good tolerance (89.6%)	55 (13HBV + 36YJV + 6WV)	24 (7HBV + 15YJV + 2WV)	67 (13HBV + 40YJV + 14WV)	87 (20HBV + 53YJV + 14WV)
Grade 1 (7.7%)	1 (= HBV)	1 (= YJV)	4 (= HBV)	14 (10HBV + 2YJV + 2WV)
Grade 2 (0.4%)	1	1 (= HBV)	0	0
Grade 3 (1.5%)	0	0	2 (= HBV)	2 (1HBV + 1YJV)
Grade 4 (0.8%)	0	0	1 (= WV)	1 (= HBV)

Grades 1 + 2 vs. grades 3 + 4 → $P = 0.016$.

Table 5. Severity of systemic reaction vs. severity of prior sting reaction in children

Side-effects of VIT Day 1 (Mueller grade)	Prior sting reaction			
	Grade 1	Grade 2	Grade 3	Grade 4
Good tolerance (90.8%)	24 (3HBV + 15YJV + 6WV)	4 (1HBV + 3YJV)	20 (4HBV + 13YJV + 3WV)	11 (4HBV + 6YJV + 1WV)
Grade 1 (3.1%)	0	0	1 (= YJV)	1 (= HBV)
Grade 2 (1.5%)	0	0	1 (= HBV)	0
Grade 3 (4.6%)	0	0	3 (= HBV)	0
Grade 4 (0.0%)	0	0	0	0

Grades 1 + 2 vs. grades 3 + 4 → $P = 0.025$.

**Fig. 1.** Threshold venom doses and systemic reactions in children (□) and adults (■).

reactors, the SR tended to occur preferentially in the patients with more positive skin tests ($0.001 \mu\text{g/mL}$; $n = 26$; Table 6).

The level of specific IgE was not related to the risk of SR whatever was the Hymenoptera species (Table 7).

The relative risk of developing systemic reaction during the rapid venom phase of immunotherapy (day 1) was evaluated. As shown in Table 8, HB venom ($P = 0.001$) and a prior sting reaction grade 3 ($P = 0.023$) or 4 ($P = 0.006$) increased the risk of developing a SR.

Age and sex were not risk factors.

Discussion

VIT is used to prevent life-threatening reactions but a remaining problem in Hymenoptera allergy is related to the safety, especially of honeybee venom immunotherapy, which may cause systemic allergic reactions in up to 20–40% of patients [19]. Different approaches to improve the safety of venom immunotherapy by changing protocols [19], by pre-treatment with antihistamines [21–23] or beekeeper gamma globulin [10], or use of chemically modified honeybee venom [24] have proved to have variable success. Defining the risk factors for SR to VIT would

be helpful in reducing the occurrence of them. This study analyses the characteristics and frequency of adverse reactions and identifies the risk factors for SR.

In our department, VIT with an ultra-rush schedule was well tolerated, on day 1, in 72.2% of 90 HB venom, in 97.3% of 186 YJ venom and in 93.9% of 49 W venom. Local reactions were observed in nearly all patients during VIT. It has to be emphasized that the majority of the SR to VIT were mild, well tolerated and either self-limiting or easily controlled by corticosteroids or oral antihistamines. Only two SR were judged severe

enough for administration of adrenaline. The higher incidence of adverse reactions in patients receiving bee VIT compared with those receiving wasp VIT is in agreement with the findings in other reports [5, 19]. The risk for SR to VIT is thus much more related to the nature of the venom than to the regimen used. It has not been elucidated why VIT with HB venom causes more SR than VIT with YJ venom. One explanation may be the differences in the strength of the extracts. In the commercial venom extracts used for VIT, YJ venom allergens are diluted in non-allergenic venom sac proteins, whereas HB venom is a purified venom with lower concentration of non-allergenic proteins [25, 26]. Reports in the literature reveal a high variation in the incidence of side-effects attributable to VIT [5]. It is difficult or even impossible to compare these reports of incidence of SR with different VIT protocols because the investigators use different classification systems for severity of adverse reactions. Rush regimens have caused SR in 13–46% of the HB venom allergics and in 0–21% of the YJ venom allergics [5, 14, 21, 27], whereas with the conventional weekly buildup regimens, frequencies of 40–46% with HB venom and of 12–25% with YJ venom have been noted [16, 17, 28]. In a previous study, we compared three different regimens (4-day, 6-h or 210-min with a cumulative venom dose of 527.6 µg, 226.6 µg and 101.1 µg, respectively), and we concluded that the rate of SR decreases with the reduction of the number of venom injections and the cumulative venom dose [14]. After a comparison with several

Table 6. Severity of systemic reaction versus degree of positive skin test

Side-effects of VIT Day 1 (Mueller grade)	Venom skin tests (µg/mL)			
	1	0.1	0.01	0.001
Good tolerance	30	21	32	202
Grade 1	2	1	1	17
Grade 2	0	0	0	2
Grade 3	0	1	0	6
Grade 4	0	1	0	1

Positive skin tests: 1+0.1+0.01 µg/mL versus positive skin tests: 0.001 µg/mL → $P=NS$. Seven patients had negative skin tests and a good tolerance, one had no skin test and a grade 1. All of them had positive sIgE.

Table 7. Severity of systemic reaction versus degree of positive sIgE (kU/mL) (CAP-RAST) geometric means and confidential intervals

	No reaction	Grade 1	Grade 2	Grade 3	Grade 4
Honeybee	2.44 (0.01–772.78)	5.16 (0.01–3714.50)	34.12 (9.30–125.21)	11.59 (1.99–67.36)	4.6
Yellow jacket	2.97 (0.02–468.72)	2.97 (0.30–29.08)		5.7	
Wasp	1.16 (0.00–361.41)	0.14 (0.00–10.18)			5.1

Table 8. Logistic regression analysis: reactor versus non-reactor patients

Variables (references)	Reactors versus non-reactors (P -value)	OR (95%CI)
Sex (male)	NS	0.82 (0.35–1.92)
Age (< 15.3 years)	NS	0.72 (0.25–2.14)
Positive skin tests (0.0 01 µg/mL)		
0.01 µg/mL	NS	0.48 (0.09–2.51)
0.1 µg/mL	NS	0.65 (0.15–2.81)
1 µg/mL	NS	0.37 (0.07–1.97)
Positive specific IgE (0–3.5 kU/L)		
3.5–17.5 kU/L	NS	1.44 (0.55–3.78)
17.5–50 kU/L	NS	1.09 (0.32–3.78)
50–100 kU/L	NS	2.23 (0.51–0.67)
Hymenoptera (Yellow jacket)		
Honeybee	0.0001	13.6 (5.08–36.49)
Wasp	NS	2.34 (0.54–10.23)
Prior sting reaction (grade 1)		
Grade 2	NS	5.3 (0.43–66.0)
Grade 3	0.023	11.7 (1.4–99.19)
Grade 4	0.006	17.99 (2.25–143.71)

protocols, from 7–9 days to 2 days, Brehler et al. concluded that the incidence and severity of adverse reactions decline if VIT dose increase protocol is shortened to 2 days [29]. Both patient-related or venom-related factors may play a role. To find out whether reactors have typical demographic or medical characteristics we compare reactors and non-reactors for age, sex, severity of the prior SR, degree of positive skin tests and positive sIgE. Our data suggest a correlation between the incidence of SR and the severity of the prior insect sting reaction, whereas the degree of positive reaction in skin tests and serum IgE concentration are not risks factors.

An EAACI-multicentre study has made it possible to collect a very large number set of data covering a variety of treatment regimens. Data from 840 patients with a total of 26 601 injections were obtained. Twenty per cent of patients had SR 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. Female sex, bee venom extract and the rapid dose increase, but not the severity of insect sting reactions, increased the risk of SR. The frequency of SR was low, and the majority of those could be managed without treatment [30]. In our study, the reactors were equally comprised of male and female patients. For one author [28], a female predominance among reactors to VIT has been observed and the reactions tended to be more severe than the reactions registered in the male group but a similar result was not found by others [16, 21].

The safety of VIT is comparable in children and adults using the same ultra-RVIT and we therefore recommend the use of ultra-RVIT in children. Such a study is unique. From the literature, we know the efficacy and safety of VIT in children [31–33] but the results were never compared with those from adults.

In conclusion, our experience with ultra-RVIT has demonstrated that it is a safe treatment for Hymenoptera anaphylaxis. The majority of SR are very mild and respond readily to properly supervised treatment. Few predictive factors were identified: bee venom VIT, increasing venom doses and severity of the prior sting reaction. In addition to its lower cost and high efficiency, safety of ultra-RVIT is an argument for using this treatment in Hymenoptera venom allergy.

Acknowledgements

We thank Eliane Gelly for her care and her attention to the patients, and Andre Lanteaume for his help in the statistical study.

References

- Lichtenstein LM, Valentine MD, Sobotka AK. Insect allergy: the state of the art. *J Allergy Clin Immunol* 1979; 64:5–124.
- Hunt KJ, Valentine MD, Sobotka AK, Benton AW, Amodio FJ, Lichtenstein LM. A controlled trial of immunotherapy in insect hypersensitivity. *New Engl J Med* 1978; 299:157–61.
- Müller U, Thurnheer U, Patrizzi R, Spiess J, Hoigné R. Immunotherapy in bee sting hypersensitivity. Bee venom versus whole-body extract. *Allergy* 1979; 34:369–78.
- Golden DBK, Kagey-Sobotka A, Valentine MD, Lichtenstein LM. Dose dependence of Hymenoptera venom immunotherapy. *J Allergy Clin Immunol* 1981; 67:370–4.
- Müller U. Insect sting allergy. Clinical picture, diagnosis and treatment. Gustav Fischer Verlag, Stuttgart 1990.
- Ramirez DA, Londono SA, Evans R. Adverse reactions to venom immunotherapy. *Ann Allergy* 1981; 47:435.
- Golden DBK, Valentine MD, Kagey-Sobotka A, Lichtenstein LM. Regimens of hymenoptera venom immunotherapy. *Ann Intern Med* 1980; 92:620–4.
- Yunginger JW, Paull BR, Jones RP, Santrach PJ. Rush venom immunotherapy program for honeybee sting sensitivity. *J Allergy Clin Immunol* 1979; 63:340–7.
- Bousquet J, Fontes A, Bobinet-Levy M, Aznar R, Michel FB. Combination of passive and active immunotherapy in the treatment of honeybee venom allergy. *J Allergy Clin Immunol* 1987; 79:947–54.
- Müller U, Morris T, Bishof M, Friedli H, Skarvil F. Combined active and passive immunotherapy in honeybee sting allergy. *J Allergy Clin Immunol* 1986; 78:115–23.
- Laurent J, Smiejan JM, Bloch-Morot E, Herman D. Safety of Hymenoptera venom rush immunotherapy. *Allergy* 1997; 52:94–6.
- van der Zwan JC, Flinterman J, Jankowski IG, Kerckhaert JAM. Hyposensitization to wasp venom in six hours. *Br Med J* 1983; 287:1329–31.
- Tarhini H, Knani J, Michel FB, Bousquet J. Safety of venom immunotherapy administered by cluster schedule. *J Allergy Clin Immunol* 1992; 89:1198–9.
- Birnbaum J, Charpin D, Vervloet D. Rapid hymenoptera venom immunotherapy: comparative safety of three protocols. *Clin Exp Allergy* 1993; 23:226–30.
- Bernstein AJ, Kagen SI, Bernstein DI. Rapid venom immunotherapy is safe routine in the treatment of patients with Hymenoptera anaphylaxis. *Ann Allergy* 1994; 73:423–42.
- Bousquet J, Menardo JL, Michel FB. Systemic reactions during maintenance immunotherapy with honeybee venom. *Ann Allergy* 1988; 61:63–8.
- Lockey R, Turkeltaub P, Olive E, Hubbard J, Baird-Warren I, Bukantz S. The hymenoptera study III. Safety of venom immunotherapy. *J Allergy Clin Immunol* 1990; 86:775–80.
- Müller U, Helbling A, Berchtold E. Immunotherapy with honeybee venom and yellow jacket venom is different regarding efficacy and safety. *J Allergy Clin Immunol* 1992; 89:529–35.
- Müller U, Mosbech H. Position paper: immunotherapy with Hymenoptera venoms. *Allergy Supplement* 1996; 48:37–46.
- Mueller HL. Diagnosis and treatment of insect sensitivity. *J Asthma Res* 1966; 3:331–3.
- Berchtold E, Maibach R, Müller U. Reduction of side effects from rush-immunotherapy with honey bee venom by pre-treatment with terfenadine. *Clin Exp Allergy* 1992; 22:59–65.
- Brockow K, Kiehn M, Reithmüller C, Vieluf D, Berger J, Ring J. Efficacy of antihistamine pretreatment in the prevention of adverse reactions to Hymenoptera immunotherapy: a perspective, randomized, placebo-controlled trial. *J Allergy Clin Immunol* 1997; 100:458–63.
- Reimers A, Hari Y, Müller U. Reduction of side-effects from ultrarush immunotherapy with honeybee by pre-treatment with fexofenadine: a double-blind, placebo-controlled trial. *Allergy* 2000; 55:484–8.
- Müller U, Rabson A, Bischof M, Lomnitzer R, Dreborg S, Lanner A. A double-blind study comparing monomethoxypolyethylene glycol modified honeybee venom and unmodified honeybee venom for immunotherapy. I. Clinical results. *J Allergy Clin Immunol* 1987; 80:252–61.
- Sanchez F, Blanca M, Miranda A et al. Comparison of *Vespula Germanica* venoms obtained from different sources. *Int Arch Allergy Immunol* 1994; 104:385–9.
- Wood C, Benson E, Timmons E, Hoffman D. Allergens in Hymenoptera venoms. X. Vespidae venoms versus venom extracts:

- comparison by two-dimensional polyacrylamide gel electrophoresis. *Ann Allergy* 1983; 51:441–5.
- 27 Gomez D, Gancedo Q, de Paramo J. Venom immunotherapy: tolerance to a 3-day protocol of rush-immunotherapy. *Allergol Immunopathol* 1995; 23:277–84.
- 28 Youlten L, Atkinson B, Lee T. The incidence and nature of adverse reaction to injection immunotherapy in bee and wasp venom allergy. *Clin Exp Allergy* 1995; 25:159–65.
- 29 Brehler R, Wolf H, Kütting B, Schnitker J, Luger T. Safety of a two-day untrush insect venom immunotherapy protocol in comparison with protocols of longer duration and involving a larger number of injections. *J Allergy Clin Immunol* 2000; 105:1231–5.
- 30 Mosbech H, Müller U. Side-effects of insect venom immunotherapy: results from an EAACI multicenter study. *Allergy* 2000; 55:1005–10.
- 31 Ponvert C, Paupe J, Scheinmann P. La désensibilisation aux venins d'hyménoptères chez l'enfant. *Rev Fr Allergo* 1997; 37:1070–7.
- 32 Rancè F, Adrover-Levy Juchet F, Brèmont F, Dutau G. Désensibilisation aux venins d'hyménoptères chez l'enfant et l'adolescent. *Rev Fr Allergo* 1994; 34:137–40.
- 33 Valentine MD, Schuberth KC, Kagey-Sobotka A, Graft DF, Kwiterovich KA, Szklo M. The value of immunotherapy with venom in children with allergy to insect stings. *N Engl J Med* 1990; 323:1601–3.