Original Article

Hymenoptera Venom Immunotherapy and Field Stings

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Abstract. *Background*: Anaphylactic sting reactions in patients with Hymenoptera venom allergy are prevented by venom immunotherapy (VIT) in most patients.
Objective: The aim of this study was to investigate re-sting reactions in the field during VIT or during an observation period of up to 13 years after cessation of treatment. Furthermore we sought to identify patients at higher risk of developing a systemic allergic reaction (SAR) and to assess possible correlations with basal serum tryptase concentration.
Methods: The clinical data of 192 patients with a recorded field sting during VIT were evaluated and the patients were questioned regarding possible re-stings after cessation of VIT. Baseline mast-cell tryptase concentrations and specific IgE were analyzed in patients with a reported SAR.
Results: Of 192 patients with reported re-stings in the field, 27 developed SARs (14.1%). A SAR occurred in 11.9% of the stings delivered during VIT, whereas 9.7% of the stings resulted in a SAR after VIT. The majority of SARs in response to a field sting during VIT were mild, whereas severe SARs occurred more often after VIT and repeated reexposure. Out of 23 patients with reported SARs, 2 (8.7%) had elevated basal serum tryptase.
Conclusions: VIT lasting for at least 3 years is effective in protecting the vast majority of patients. The individual predictability of the response of patients to a field sting is low. SARs of increased severity mainly occur after therapy and after tolerating consecutive stings.

Key words: Field sting. Hymenoptera venom allergy. Mast cell tryptase. Systemic allergic reaction. Venom immunotherapy.

Resumen. *Antecedentes*: Las reacciones anafilácticas por picaduras en los pacientes con alergia al veneno de himenópteros se pueden prevenir en la mayoría de los casos con la administración de inmunoterapia con veneno (ITV).
Objetivo: El propósito del estudio fue investigar las reacciones a nuevas picaduras espontáneas durante la ITV o durante un período de observación de hasta 13 años después del cese del tratamiento. Asimismo, perseguimos el objetivo de identificar a los pacientes con un mayor riesgo de desarrollar una reacción alérgica sistémica (RAS) y analizar las posibles correlaciones con la concentración de triptasa sérica basal.
Métodos: Se evaluaron los datos clínicos de 192 pacientes que recibieron picaduras espontáneas durante el seguimiento de la ITV y se entrevistó a los pacientes para averiguar si habían recibido nuevas picaduras tras dejar esta terapia. Se analizaron las concentraciones de triptasa en mastocitos e IgE específica de referencia en pacientes con RAS declarada.
Resultados: De 192 pacientes con nuevas picaduras espontáneas, 27 presentaron RAS (14,1%). La RAS ocurrió en un 11,9% de las picaduras realizadas durante la ITV, mientras que un 9,7% de las picaduras dieron lugar a una RAS después de la terapia. La mayoría de RAS derivadas de respuestas a una picadura espontánea durante la ITV fueron leves, mientras que las RAS graves ocurrieron con más frecuencia después de la ITV y tras repetidas exposiciones. De 23 pacientes con RAS declaradas, 2 (8,7%) tuvieron niveles elevados de triptasa sérica basal.
Conclusiones: La ITV de 3 años de duración como mínimo es eficaz para proteger a la gran mayoría de pacientes. La capacidad de predecir la respuesta individual a una picadura espontánea es baja. Las RAS con aumento de la gravedad ocurren principalmente después de la terapia y tras tolerar diversas picaduras.

Palabras clave: Picadura espontánea. Alergia al veneno de himenópteros. Triptasa en mastocitos. Reacción alérgica sistémica. Inmunoterapia con veneno.

Introduction

Systemic allergic reactions (SARs) to Hymenoptera stings are reported in about 0.8% to 5% of the general population [1]. In Austria, these reactions are mainly caused by honeybees (*Apis mellifera*), yellow jackets (*Vespula germanica* and *Vespula vulgaris*), and less commonly by bumble bees (*Bombus* species) and European hornets (*Vespa crabo*). Venom immunotherapy (VIT) has been shown to be effective in preventing further systemic anaphylactic sting reactions in patients with Hymenoptera venom allergy [2-3]. There is general agreement that VIT should be continued for at least 3 to 5 years [4-5]. However, protection is not achieved in all patients. The percentage of patients found not to be protected against re-stings varies between different studies and treatment schedules [4, 6-12]. In most of the studies, sting challenge tests were performed to determine the efficacy of VIT and to assess the risk of systemic sting reactions to a subsequent field sting [6-7, 13-14]. However, it still remains unclear whether sting challenges can reliably predict a field sting reaction [4, 15]. It has also been suggested that elevated baseline serum tryptase levels and/or mastocytosis may be associated with increased severity of the anaphylactic reaction after a sting and reduced efficacy of VIT [16-18].

In this study, we addressed the outcome of field stings occurring in 192 patients up to 13 years after completion of at least 3 years of VIT. In addition, we analyzed the efficacy of VIT in relation to baseline serum tryptase concentration in patients who developed SARs after a field sting.

Methods

Patients

All patients receiving VIT in our department between 1982 and 2003 were questioned by a physician during their treatment regarding possible field stings and 192 patients were identified with a recorded field sting. These patients were included in a retrospective, descriptive study. The hospital records of the patients were evaluated and all 192 patients were contacted by telephone to ask about possible re-stings.

Atopic disposition was diagnosed on the basis of elevated total serum IgE levels (>100 kU/L). Data were available on 69 patients, of which 29 displayed atopic disposition.

Venom Immunotherapy

All patients were treated with bee or yellow jacket venom (ALK-Abelló, Horsholm, Denmark). VIT was started on an inpatient basis using a modified conventional protocol, reaching a dose of 6 μg after the first 3 days. Thereafter, the dose was gradually increased by injections every 1 to 2 weeks, reaching a final maintenance dose of 100 μg after 7 to 14 weeks. The maintenance dose was administered every 4 to 8 weeks over a period of at least 3 years.

Skin Tests

Standardized end-point titration skin prick tests with purified venom extract solutions (ALK-Abelló; 1, 10, and 100 μg/mL until October 1995 and 10, 100, and 300 μg/mL from October 1995 to date) were performed along with intradermal tests (0.01, 0.1, and 1 μg/mL) prior to therapy.

Venom-Specific IgE Antibodies

Venom-specific IgE antibodies were analyzed before therapy by radioallergosorbent test (Phadezym, Pharmacia Diagnostics, Uppsala, Sweden) or IgE immunoassay (immuno-CAP, Pharmacia Diagnostics) according to the manufacturer's recommendations. IgE concentrations were grouped into RAST classes defined by the manufacturer: class 1, 0.35- 0.69 kU/L; class 2, 0.70- 3.49 kU/L; class 3, 3.50-17.49 kU/L; class 4, 17.5-50 kU/L; class 5, 50-100 kU/L; class 6, >100 kU/L.

Patients with reported systemic allergic re-sting reactions were called in during 2003 and venom-specific IgE antibodies were analyzed.

Measurement of Mast-Cell Tryptase Concentration

Blood samples from patients with reported systemic allergic re-sting reactions called in during 2003 were used to measure baseline mast-cell tryptase concentrations with a fluoroenzyme immunoassay (UniCAP Tryptase, Pharmacia Diagnostics). Assays were performed according to the manufacturer's protocol. Tryptase concentrations of greater than 20 μg/L were considered to be elevated.

Statistical Analysis

All statistical analyses were performed using GraphPad Prism software (GraphPad Software Inc, San Diego, USA). Differences in age at the first recorded field sting between individuals allergic to bee and yellow jacket venom were compared by unpaired Student *t* test. *P* values less than .05 were considered statistically significant.

Results

A total of 192 patients (121 men and 71 women) with reported field stings during or after VIT of at least 3 years were included in the study. The mean age at the time of the first field sting during or after VIT was 31.7 years (range, 3 to 78 years). Clinical data are shown in Table 1.

Table 1. Clinical and Demographic Data for Patients With a Reported Field Sting During or After Venom Immunotherapy*

	BV Allergy	YJV Allergy	BV/YJV Allergy
Number of patients	95 (49.5%)	64 (33.3%)	33 (17.2%)
Age at first recorded field sting, y, mean (range)	25.1 (5-68)†,‡	39.9 (5-76)	34.8 (3-78)
Sex, M/F	61/34	38/26	22/11
Pre-treatment skin test reaction			
Prick: 300 µg/mL	8	6	1/4
100 µg/mL	36	29	13/15
10 µg/mL	23	9	7/3
1 µg/mL	6	4	3/2
Negative	20	13	9/8
Not available	2	3	0/1
Intradermal: 1.0µg/mL	19	12	3/7
0.1 µg/mL	20	20	9/10
0.01 µg/mL	38	20	13/9
Negative	1	4	3/2
Not available	17	8	5/5
Pretreatment specific serum IgE			
Class 0	1 (1.1%)	5 (7.8%)	0/1
Class 1-2	25 (26.3%)	29 (45.3%)	13/24
Class 3-4	61 (64.2%)	25 (39.1%)	18/7
Class 5-6	7 (7.4%)	3 (4.7%)	1/0
Not available	1 (1.1%)	2 (3.1%)	1/1

* Data are shown as number (%) unless otherwise indicated; BV indicates bee venom; YJV, yellow-jacket venom; M, male; F, female. † $P < .0001$ vs patients with YJV allergy; ‡ $P < .05$ vs patients with BV/YJV allergy; unpaired *t* test.

Table 2. Clinical and Demographic Data for Patients With a Systemic Allergic Reaction after a Field Sting During or After Venom Immunotherapy*

	BV Allergy	YJV Allergy	BV/YJV Allergy
Number of patients	17	7	3
Age at first recorded field sting with SARs, y, mean (range)	33.1 (11-80)†	55.0 (41-76)	46.3 (35-62)
Sex, M/F	10/7	4/3	0/3
Pre-treatment skin test reaction			
Prick: 300 µg/mL	2	–	–
100 µg/mL	7	4	2/3
10 µg/mL	4	1	1/0
1 µg/mL	2	–	–
Negative	2	2	–
Intradermal: 1.0µg/mL	2	2	–
0.1 µg/mL	3	3	1/1
0.01 µg/mL	9	1	0/2
Negative	–	1	2/0
Not available	3	–	–
Pretreatment specific serum IgE			
Class 0	–	–	–
Class 1-2	5 (29.4%)	4 (57.1%)	1/1
Class 3-4	9 (52.9%)	2 (28.6%)	2/2
Class 5-6	2 (11.8%)	1 (14.3%)	–
Not available	1 (5.9%)	–	–

* Data are shown as number (%) unless otherwise indicated; BV indicates bee venom; YJV, yellow-jacket venom; M, male; F, female. SAR, systemic allergic reaction. † $P < .05$ vs patients with YJV allergy, unpaired *t* test.

Ninety-five patients (49.5%) were treated with honeybee venom (BV) and 64 (33.3%) with yellow jacket venom (YJV). Thirty-three patients (17.2%) were vaccinated with both venoms. Interestingly, patients treated with BV were significantly younger when a field sting was reported (mean age±SD, 25.1 ±17.7 years) compared with patients receiving YJV therapy (39.9±17.8 years; $P < .0001$) and patients receiving combined therapy (34.8±21.4 years; $P < .05$). The pretreatment venom-specific serum IgE concentration tended to be lower in patients with YJV

Table 3. Patients Reacting Systemically to Field Stings During or After Venom Immunotherapy*

Patient	Sex	Age†	Severity of Reaction‡	Year of VIT	Years After VIT	Further Fieldstings Without SAR
BV sensitive						
1	F	57	II	3		No
2	F	30	III	1		No
			III	2		
3	F	62	II	1		Years 2 and 3 of VIT
			II	1		Years 1 and 2 after VIT (> 10 stings)
			I	1		
			II	1		
4	M	34	I	3		No
			I		4	
5	F	16	I		3	No
6	M	13	I	2		Year 1 of VIT
						Year 3 of VIT
						Year 2 after VIT
7	M	30	III		4	Year 1 of VIT (2 stings)
8	F	11	I	2		No
9	M	46	I	1		No
10	F	39	I	1		Year 2 of VIT
			I	1		
			I	1		
11	M	19	III		8	Year 2 after VIT
12	M	28	III		10	Year 4 after VIT
13	M	29	I	1		Year 2 of VIT,
			III		8	Year 3 of second VIT
14	F	80	I		13	Year 1 of VIT
15	M	38	III		13	After VIT (10 stings)
16	M	19	I	3		No
17	M	11	I	3		Year 2 of VIT
YJV sensitive						
18	M	51	I	2		No
19	F	76	I	2		No
20	M	55	III	2		No
21	F	54	II	1		Year 3 of VIT
22	F	44	II	1		Year 3 of VIT
23	M	64	III		11	Years 7, 9, and 11 after VIT
24	M	41	III	2		nd
BV/YJV sensitive						
25	F	42	I	2		No
			I	4		
			IV		1	
26	F	62	I	3		No
			II	4		
27	F	35	II	2		No

* BV indicates bee venom; YJV, yellow-jacket venom; M, male; F, female; SAR, systemic allergic reaction; VIT, venom immunotherapy; nd, not determined.
† Age at the first recorded field sting with SAR; ‡ Classified according to Mueller [19].

therapy. Twenty-five patients (26.0%) with BV allergy had class 1 and 2 levels and 62 patients (64.6%) class 3 and 4 levels, whereas in patients treated with YJV 30 patients (46.2%) had class 1 and 2, and 25 (38.5%) class 3 and 4 venom-specific pretreatment serum IgE levels. The total number of field stings recorded was 367, some patients having been stung several times. Two hundred and fourteen stings (58.3%) were delivered by honeybees and 120 by yellow jackets (32.7%). In 33 cases (9.0%) the insect was not identified. Two hundred and nineteen stings occurred after VIT (65.8%) and 93 stings were observed during VIT (27.8%). The timing of the sting was unknown in 22 cases (6.6%).

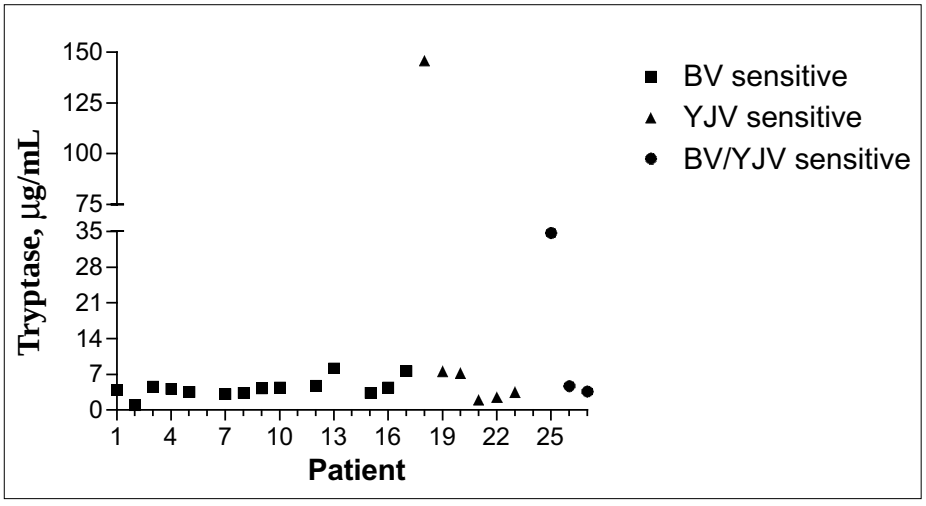
Of the 95 patients allergic to BV, 56 patients were stung during VIT and 8 of those developed SARs, while 4 of the 8 patients reporting a sting after VIT developed SARs. Twenty-four patients received a bee sting in the field both during and after VIT (3 SARs reported for each period). These results correspond to reaction rates of 13.8% (11 SARs from 80 patients stung) during VIT and 21.9% (7 out of 32) after VIT. Seven patients did not know the exact date of the re-sting. Of the 64 patients allergic to YJV, 43 reported stings during VIT with 6 patients reacting systemically, and 3 patients were stung after VIT resulting in 1 SAR. No SARs were observed in the 13 patients stung both during and after VIT. Thus, the reaction rates for yellow-jacket allergic patients were 10.7% (6 SARs from 56 patients stung) during VIT and 6.3% (1 out of 16) after VIT. For 5 patients with YJV allergy the exact date of the re-sting could not be determined. Two of the 19 patients vaccinated with both venoms still reacted systemically to a field sting during VIT, whereas 1 patient stung only after VIT tolerated the sting without a SAR. Twelve patients were stung both during and after VIT, with the same patient developing a systemic reaction during and after VIT. Thus, relapse rates of 9.7% (3 SARs from 31 patients stung) during VIT and 7.7% (1 out of 13) after VIT were recorded in this subgroup of patients. Two patients were unable to provide the date of the re-sting. Clinical data on VIT patients with a systemic reaction after a field sting are presented in Table 2.

Patients who developed SARs in response to a re-sting were significantly younger in the group that received BV treatment (33.1 ± 19.3 years) than in the group that received YJV treatment (55.0 ± 11.9 years; $P < .05$). In patients who developed SARs, higher pretreatment venom-specific serum IgE levels were observed in patients vaccinated with BV (29.4% class 1 and 2, 52.9% class 3 and 4) than in patients with YJV therapy (57.1% class 1 and 2, 28.6% class 3 and 4). Out of 312 stings with known date and insect, 35 stings (11.2%) led to a systemic reaction. A total of 11.9% of the stings delivered during VIT (26 out of 219) caused a SAR, whereas 9.7% of the stings after VIT resulted in a SAR (9 out of 93). Out of a total of 141 bee stings during VIT, 16 (11.3%) resulted in a SAR; the same frequency was observed after VIT (7 SARs out of 62 stings, 11.3%).

Different relapse rates were observed for yellow-jacket stings. Whereas 10 out of 78 stings (12.8%) during VIT resulted in a SAR, only 2 out of 31 stings (6.5%) led to a SAR after discontinuation of VIT.

Table 3 shows details of the re-sting reactions in 17 individuals allergic to BV, 7 individuals allergic to YJV, and 3 individuals allergic to both venoms. In 7 patients (25.9%), the first reaction occurred after a re-sting during the first year of VIT, in 8 (29.6%) during the second year of VIT, in 5 (18.5%) during the third year of VIT, and in 7 patients (25.9%) 3 to 13 years after discontinuation of therapy. Thirteen patients had only 1 re-sting with SARs during VIT. Seven patients reacted systemically to a re-sting after VIT. The majority of systemic sting reactions occurred during VIT (28 of 38). Based on the symptom classification of Mueller [19], the majority of those reactions (85.7%) were associated with mild symptoms (grade I or II), while only 4 SARs occurring during therapy (14.3%) were severe (grade III or IV). In contrast, 7 out of 10 (70%) of the SARs that developed after VIT were severe and only 3 (30%) had mild symptoms.

To assess whether a history of SARs after a field sting



Baseline serum mast-cell tryptase concentration in patients allergic to Hymenoptera venom who developed SARs to a field sting during or after VIT.
BV indicates bee venom; YJV, yellow jacket venom.

during or after VIT is correlated with elevated baseline tryptase levels, we analyzed serum tryptase concentrations in 23 patients. Only 2 out of 23 patients (8.7%; patients 18 and 25) had raised baseline serum tryptase concentrations (figure). Patient 18 was diagnosed with cutaneous mastocytosis, which was histologically confirmed by skin biopsy. Systemic involvement was ruled out by clinical follow-up including bone marrow biopsy.

Discussion

VIT is an established and widely used therapy for the treatment of Hymenoptera venom allergy. It is generally agreed that a minimum of 3 years is necessary to protect most patients [4,5]. Here, we have described 192 patients allergic to Hymenoptera venom who received 219 field stings during VIT and 93 field stings up to 13 years after completion of at least 3 years of VIT.

Müller et al [20] reported 23% of patients with BV allergy reacting to a sting challenge during VIT and a significantly lower reaction rate (9%) in patients allergic to YJV. In contrast, in our study reaction rates to a field sting during VIT were only slightly different between patients with allergy to BV and those allergic to YJV (13.8% vs 10.7%). The percentage of patients still reacting systemically to a re-sting after cessation of VIT varies considerably between different studies. The differences in the efficacy of VIT between the studies seem to be related to patient selection criteria such as venom type, severity of previous sting reactions, age, and indications for initiation and cessation of therapy, as well as different treatment protocols and observation periods [4, 6-9, 13, 21-22]. Haugaard et al [23] reported no systemic reaction after 28 sting challenges in 25 adults who had received VIT for a mean period of 42.8 months. In another study, SARs after a sting challenge occurred only in 2 out of 117 patients (2%) who had mostly received 4 to 6 years of VIT [24]. However, a higher incidence of SARs was observed by Van Halteren et al [7], with an overall relapse rate of 8% after a sting challenge in patients with VIT given for a median duration of 40 months. In our study, field stings up to 13 years after completion of at least 3 years of VIT resulted in an overall relapse rate of 14.8%. This observation is comparable to the results of Golden et al [11], who reported SARs in 14% of patients after discontinuation of VIT of at least 5 years. Our observations that patients with BV immunotherapy tend to have a higher frequency of treatment failures and relapses than patients with YJV immunotherapy are also consistent with the findings of other authors [4, 20]. The low relapse rate of 6.3% after stopping VIT in patients allergic to YJV is in accordance with the findings of Lerch and Müller [4], where 7.5% of the patients exhibited re-sting reactions. In contrast, the relapse rate in individuals allergic to BV was higher in our study (21.9%) than in the study of Lerch and Müller [4] (15.8%) or that of Müller et al [13] (17%). Although 5 of the 17 BV-allergic patients who exhibited SARs after a field sting during VIT received lower maintenance doses because of side effects during therapy (80 μg in patients 3, 6, and 8, and 60 μg in patients 2 and 4) and the maintenance dose was 100 μg in all YJV-allergic patients with SARs, this is not sufficient to explain the observed differences in the efficacy of VIT after termination, since only 1 of the 5 patients (patient 4) also reacted systemically after stopping VIT. The observed higher pretreatment venom-specific serum IgE levels in patients vaccinated with BV could be a possible explanation for the different relapse rates. Differences in the protein content between honey bees and yellow jackets might also account for the difference in the results [25]. Interestingly, patients with BV treatment were significantly younger than patients with YJV treatment at the time a field sting was reported, as well as at the time SARs occurred, although younger patients seem to be at lower risk of a repeated systemic reaction [26,27].

The majority of SARs occurring in response to a field sting during VIT were mild, whereas after VIT severe SARs occurred more often. Our data show that a tolerated field sting during or after VIT does not necessarily ensure future safety. Even fatalities have been reported following a previously tolerated field sting after stopping VIT [28]. The low individual predictability of the response of patients to a field sting is illustrated by the cases of patients 13 and 23 (Table 3). Our data are also consistent with observations that SARs after stopping VIT may occur predominantly after repeated exposure [4, 11, 29].

Obviously, there are differences in the assessment of relapse risk between in-hospital sting challenges and field stings, and the reliability of in-hospital challenges to determine the efficacy of VIT is still a matter of debate [15, 30]. However, data on field stings should be interpreted with caution because they are subject to some uncertainty in their identification. It also can not be ruled out that some field stings could not be recalled by our patients. An important issue associated with field stings is the marked influence of subjective interpretation of a reaction, which can be more objectively assessed in a hospital setting.

Reports of a possible correlation between the severity of SARs to Hymenoptera stings and elevated serum mast-cell tryptase in those patients [17-18] prompted us to analyze the basal serum concentrations of mast-cell tryptase in patients with SARs during or after VIT. Only 8.7% of the patients reacting with SARs to a field sting had elevated basal serum tryptase. A similar number was reported by Haeberli et al [18], where 9.8% of the patients systemically reacting to a sting challenge had increased serum tryptase concentrations. Moreover, those authors observed not only a significantly higher number of individuals with elevated basal tryptase levels associated with allergy to YJV than BV, but also more SARs to sting challenges with yellow jackets in those patients. In this study, the 2 patients with raised baseline serum concentration of mast-cell tryptase developed SARs after

being stung by yellow jackets, but this number is too small to draw final conclusions. In our study, the interval between sting reaction and testing was several years in some patients; however, elevated tryptase levels have been reported to remain stable for at least 3 years [31]. Increased tryptase levels are also associated with mastocytosis [17, 31], and this diagnosis was histologically confirmed by skin biopsy in 1 of our patients with elevated basal serum tryptase. Evidently, although VIT has been found to be effective in patients with mastocytosis [32], even fatal SARs still can occur [16]. It is not known if continued lifelong treatment as well as increased venom doses can fully protect patients with mastocytosis, but it has been suggested that increased venom doses will be more effective in the treatment of Hymenoptera allergy [12].

In conclusion, our results show that VIT lasting at least 3 years is effective in protecting the vast majority of patients over an observation period of up to 13 years. SARs of increased severity predominantly occur after therapy and after tolerating consecutive stings. The individual predictability of the response of patients to a field sting is low, and VIT does not necessarily ensure future safety.

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