

Safety and effectiveness of immunotherapy in patients with indolent systemic mastocytosis presenting with Hymenoptera venom anaphylaxis

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Background: Anaphylaxis after Hymenoptera sting has been described in patients with mastocytosis. Venom immunotherapy (VIT) is a safe and effective way to treat patients with Hymenoptera anaphylaxis, but few studies have addressed its usefulness in patients with systemic mastocytosis.

Objective: To study the effectiveness and safety of VIT in patients with systemic mastocytosis having anaphylaxis after Hymenoptera sting.

Methods: A total of 21 mastocytosis patients—4 women (19%) and 17 men (81%) with a median age of 50 years (range, 29-74 years)—with Hymenoptera sting anaphylaxis who were treated with VIT and followed for a median of 52 months (range, 2-250 months) were studied.

Results: In 18 of 21 patients—16 of them lacking skin involvement—anaphylaxis was the presenting symptom. Six patients (29%) experienced adverse reactions during VIT, 3 during initiation and 3 during maintenance. Twelve patients (57%) were resting while undergoing VIT; 9 (75%) presented

local reactions and 3 (25%) systemic reactions, 1 of which required intubation. The Hymenoptera specific IgE decreased from 4.15 kU/L (range, 0.44-100 kU/L) before immunotherapy to 1.2 kU/L (range, 0.34-69.4 kU/L) after 4 years ($P < .003$).

Conclusion: Venom immunotherapy is effective to treat IgE-mediated Hymenoptera anaphylaxis in patients with mastocytosis. Its use is recommended despite a relatively high risk of adverse reactions during the build-up phase because it provides protection from anaphylaxis in around 3/4 of the patients.

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Key words: Anaphylaxis, effectiveness, Hymenoptera, immunotherapy, mastocytosis, safety, skin lesion, tryptase, venom

In a recent study reporting on a cohort of 163 adults with mastocytosis, Hymenoptera venom anaphylaxis (HVA) was found in 8 cases (5%).¹ In previous reports, Hymenoptera anaphylaxis has been described mainly in indolent systemic mastocytosis (ISM) with cutaneous involvement and only a few patients lacking skin lesions.²⁻⁴ The association between HVA and an increase in baseline tryptase (BT) has been reported in 19 of 259 cases (7.3%),^{5,6} and it has been considered a risk factor for severe or nearly fatal reactions.⁵

Venom immunotherapy (VIT) is a safe and effective way to treat individuals with systemic reactions, preventing morbidity and mortality from a subsequent sting reaction.⁷ Indications for immunotherapy include a clinical history of a systemic allergic reaction after a Hymenoptera sting and the presence of circulating venom specific IgE antibodies and/or positive skin test results. VIT for 3 to 5 years induces long-term protection in most patients.⁵ So far, few studies have addressed the usefulness of VIT in patients with mastocytosis. The most relevant one includes 10 patients with urticaria pigmentosa in whom no side effects during VIT were described and only 1 patient presented a mild systemic reaction after resting or sting challenge.⁸ VIT in mastocytosis has been reported to be effective^{5,8-10} and proposed as a treatment for life,^{5,8} but cases of fatal reactions after VIT have also been described.^{11,12} So far, no study has investigated the risk of discontinuation of VIT for patients with severe anaphylaxis and mastocytosis, but at least 2 fatalities have been reported after VIT was discontinued.¹¹

The aim of this study is to investigate the effectiveness and safety of VIT in patients with mastocytosis. For that purpose, we performed an observational and retrospective study on 21 adults with mastocytosis and HVA undergoing VIT who were referred to

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Abbreviations used

BM:	Bone marrow
BT:	Baseline tryptase
EPC:	End-point concentration
HVA:	Hymenoptera venom anaphylaxis
ISM:	Indolent systemic mastocytosis
MC:	Mast cell
REMA:	Red Española de Mastocitosis
SM:	Systemic mastocytosis
UP:	Urticaria pigmentosa
VIT:	Venom immunotherapy

the Spanish Network on Mastocytosis (Red Española de Mastocitosis [REMA]).

METHODS**Patients**

A total of 21 patients with HVA undergoing immunotherapy were selected. Recruitment of patients was performed as follows: (1) 3 patients were registered at the REMA with a diagnosis of systemic mastocytosis (SM) at the time of the anaphylactic event, and (2) 18 were referred to the REMA for suspected mastocytosis because of elevated BT after the anaphylactic event. There were no formal exclusion criteria, but an 8-year-old boy with Hymenoptera sting anaphylaxis and elevated BT was excluded because there was no indication for a bone marrow (BM) study.

The study was approved by the Ethical Committees of each referring center—Hospital Ramón y Cajal (Madrid, Spain), Hospital Virgen del Valle (Toledo, Spain), and Brigham and Women's Hospital (Boston, Mass)—and all patients signed an informed consent form before entering the study.

Skin tests

Skin tests were performed in 20 patients with venoms of yellow jacket (*Vespa* spp), paper wasp (*Polistes* spp), and honey bee (*Apis mellifera*) (Pharmalgen; ALK Allergologisk Laboratorium A/S, Hørsholm, Denmark; or Allergovac; Bial-Aristegui, Bilbao, Spain) and also with white-faced hornet and paper hornet in 1 patient (Greer Laboratories, Lenoir, NC). Intracutaneous tests were performed starting with concentrations ranging from 0.001 to 0.01 μ g/mL with 10-fold increments until a positive reaction occurred or a maximum concentration of 1.0 μ g/mL was reached. An intracutaneous test was considered positive when a wheal ≥ 5 mm in diameter with erythema was obtained after 20 minutes of its performance. The end-point concentration (EPC)—the lowest concentration that results in a positive reaction—was used to measure the skin sensitivity to venoms. An EPC equal to or less than 0.1 μ g/mL was considered positive, an EPC of 1.0 μ g/mL doubtful, and an EPC >1.0 μ g/mL negative, because of nonspecific skin irritation.¹³

Serum determinations: BT, total IgE, and venom-specific IgE antibodies

Skin tests, venom-specific IgE, and BT were performed as part of routine patient care. BT levels were measured since 1993, when the technique became available and both total serum IgE levels and venom-specific IgE levels were measured by using a commercially available kit by the CAP system (Pharmacia Diagnostics AB, Uppsala, Sweden).

A control population (50 patients from the Ramón y Cajal Hospital, age 2–70 years) was used to measure levels of serum total IgE. Their median IgE value was 45 IU/mL (range, 2–65 IU/mL), and BT values were constantly <10 ng/mL. A specific IgE test was considered positive for values >0.35 kU/L.

VIT

Prescription of immunotherapy (and its composition) was indicated by the patient's allergist. VIT was administered following the recommendations of

the European Academy of Allergy and Clinical Immunology subcommittee on insect venom allergy,¹⁴ using the conventional protocol¹⁵ according to the patient's allergist's criteria. A cluster protocol, which reaches maintenance doses in 2 to 5 weeks, was also followed. Pharmalgen (ALK Allergologisk Laboratorium A/S), Allergovac (Bial-Aristegui, Bilbao, Spain) or Greer Laboratories extract venoms were used. Maintenance doses were usually administered monthly. Over the second year of VIT, the time interval of injection was elapsed in some of the patients, following the indications of the patient's allergist. Requirement for medication before the injection of VIT was also recorded.

Safety was judged from the rate of occurrence of allergic symptoms after VIT injections. No sting challenges were performed.

Diagnosis of mastocytosis

Diagnosis of mastocytosis was based on a complete clinical and physical work-up, routine peripheral blood counts and differential, routine biochemistry and serum tryptase levels. Skin biopsy was performed in all cases with suspected cutaneous involvement. A BM study was performed following previously established methods and criteria for morphology,¹⁶ histology, and immunohistochemistry,^{17,18} flow cytometry,^{19,20} and c-kit mutational studies.^{21,22} Classification of mastocytosis followed the World Health Organization guidelines.^{23–25}

Study design

Skin tests, BT, serum total IgE, and venom-specific IgE antibodies were systematically assessed after the anaphylaxis episode and before VIT. Patients were selected for VIT on the basis of the presence of positive skin tests and/or venom-specific IgE antibodies. Once the administration of VIT was initiated, annual determinations of all the aforementioned parameters were performed.

In addition, clinical symptoms directly related to mastocytosis such as pruritus, flushing, gastrointestinal and neuropsychiatric symptoms, and the need for antimediation therapy were recorded.

Statistical methods

Data on continuous variables are presented as medians and ranges, and crude analyses were performed by using the Mann-Whitney *U* test because distribution of data departed from normality. Categorical and continuous variables were compared by using the nonparametric χ^2 and Wilcoxon tests, respectively (SPSS v15.0; SPSS Inc, Chicago, Ill). *P* values $<.05$ were considered statistically significant.

RESULTS**General characteristics of patients**

A total of 21 adults—4 women (19%) and 17 men (81%) with a median age of 50 years (range, 29–74 years)—diagnosed with ISM were analyzed.²⁴ Both the clinical characteristics and the required antimediation therapy are detailed in Table I for each patient. In 18 of 21 patients (86%), including 2 patients with skin lesions, anaphylaxis was the presenting symptom. In these patients, the diagnosis of mastocytosis was made after the episode of anaphylaxis (median, 48 months; range, 0–243 months).

Clinical data after Hymenoptera sting anaphylaxis

In 16 patients (76%) the Hymenoptera responsible of the anaphylaxis was a wasp; paper wasp (*Polistes* spp) seemed to be the agent in 7 patients and yellow jacket (*Vespa* spp) in 6 cases, according to the skin tests and specific IgE values. In the remaining 3 patients with wasp sting anaphylaxis, an accurate identification was not possible. In the other 5 patients (24%), anaphylaxis occurred after a honeybee sting (*Apis mellifera*).

TABLE I. Clinical characteristics of patients

Patient no.	Age (y)	Sex	Type of SM	Skin lesion	Time from anaphylaxis to diagnosis of SM* (mo)	MC mediator-related symptoms	Treatment of SM
1	50	Male	ISM	No	48	None	dc
2	33	Female	ISM	No	9	GI	dc
3	45	Male	ISM	UP	Previous† (60)	GI, S, N	dc,h1 prn
4	59	Male	ISM	No	66	None	dc
5	49	Female	ISM	UP	Previous† (276)	GI, S, N	dc,h1,h2
6	55	Female	ISM	No	190	None	dc
7	39	Male	ISM	UP	Previous† (130)	S	dc, h1 prn
8	54	Male	ISM	No	10	None	dc
9	46	Male	ISM	No	33	None	dc
10	37	Male	ISM	No	60	None	dc
11	40	Male	ISM	No	60	None	dc
12	73	Male	ISM	No	24	None	dc
13	74	Male	ISM	No	240	GI	dc
14	29	Male	ISM	No	120	None	dc
15	45	Male	ISM	No	102	None	dc
16	52	Male	ISM	No	243	None	dc, h1 prn
17	51	Male	ISM	No	36	None	dc
18	61	Male	ISM	UP	156	BP, GI, R, S	dc,h1,h2
19	55	Male	ISM	N	11	None	dc
20	59	Female	ISM	N	84	None	dc
21	49	Male	ISM	TMEP	24	GI, N	dc,h1

BP, Reduced blood pressure documented by a medical professional; dc, disodium cromoglycate; GI, gastrointestinal symptoms (including peptic disease, abdominal cramping, diarrhea); h1, antihistamines; h2, histamine H2-receptor antagonist; N, neuropsychiatric symptoms (concentration difficulties, irritability, insomnia, anxiety, depression); prn, *pro re nata* or as needed; R, respiratory symptoms (dyspnea, wheeze-bronchospasm, stridor); S, involvement of skin-mucosal tissue (pruritus); TMEP, telangiectasia macularis eruptiva perstans.

*Time elapsed between anaphylaxis after Hymenoptera sting and diagnosis of mastocytosis (expressed in months).

†Mastocytosis diagnosis performed before the episode of anaphylaxis after Hymenoptera sting (number of months).

Symptoms experienced after the sting and its lag time are shown in Table II. Sixteen patients of 21 (76%) reported feeling of impending doom after the sting. Fourteen patients (63%) required epinephrine as a treatment to the reaction. No fatalities were reported.

The results of the *in vitro* and *in vivo* tests which led to the diagnosis of allergy to Hymenoptera—intracutaneous tests and/or specific IgE to the Hymenoptera, total IgE and BT—are also shown in Table II whenever performed at the same moment.

Immunotherapy injection, adverse reactions to VIT, and resting

Among the 21 patients, 7 underwent *Polistes* immunotherapy, 6 received *Vespula* immunotherapy, 5 received *Apis* immunotherapy, 2 went through 2 different types of VIT (*Vespula* and *Polistes* separately), and 1 patient received vespid venom and honeybee immunotherapy mixed together. All the injections were performed in a monitored setting with skilled personal and with available emergency treatment and equipment, according to the recommendations of the European Academy of Allergy and Clinical Immunology.¹⁴ For those patients who had presented a systemic adverse reaction during VIT ($n = 6$) or a systemic reaction after resting ($n = 3$) the first dose or the dose after an anaphylactic reaction was administered in the Intensive Care Unit.

The VIT protocol used is described in Table III. Maintenance doses of 100 μ g were administered in 20 of 21 patients, and doses of 300 μ g of mixed vespid venom together with 100 μ g of honeybee venom were administered to the remaining patient. Among those 20 patients who received doses of 100 μ g, 2 tolerated the maintenance doses after changing from

Pharmalgen extract to Aquagen SQ (ALK Allergologisk Laboratorium A/S, Hørsholm, Denmark), an amine-free extract, and premedication with antihistamines, 10 mg of prednisone, and antileukotrienes before injection, during the initiation phase. In 1 of these 2 patients, serum tryptase values increased from 13.5 ng/mL before the injection to 33 ng/mL 2 hours later. Nevertheless, the patient remained asymptomatic. In the 2 patients undergoing 2 separate VIT sessions, maintenance doses were administered monthly, alternating every 15 days. Fourteen of 21 patients received maintenance injections monthly during the complete duration of the VIT. The remaining 7 patients received monthly injections for 24 months. The doses were then elapsed to every 6 to 12 weeks, depending on the criteria of their allergist.

Six patients of 21 (29%) experienced adverse reactions during VIT injections, 3 during initiation and 3 during maintenance doses. Both the clinical characteristics of the reactions and the medication used before VIT are detailed in Table III. When an adverse reaction occurred, the next dose to administer was repeated or slightly decreased. All these patients but 2 continued with VIT after the reaction—patient 12 refused to continue on VIT, whereas in patient 21, VIT was stopped because of the severity of the reactions.

Eight of the 21 patients in the study (38%) were rural and thus were at higher risk of Hymenoptera sting. Twelve patients (57%) were resting while undergoing VIT, 11 during the maintenance phase and 1 during initiation. Among these patients, 9 of 12 (75%) presented local reactions and 3 of 12 (25%) systemic reactions (Table III). The patient resting during initiation experienced a systemic reaction and a cardiac arrest that required endotracheal intubation.

TABLE II. Clinical data of patients after Hymenoptera sting

Patient no.	Symptoms at sting	Lag time (min)	Impeding doom*	Time to diagnosis (mo)†	Skin tests‡ Hym. (μg/mL)	Total IgE (UI/mL)	Specific IgE§ Hymenoptera (kU/L)	Serum BT (ng/mL)
1	BP, R, S	15-20	No	2	v (0.001) p (0.1)	104	v (17.5) p (10.5)	29.1
2	BP, R, S	10	Yes	2	v (0.1)	81	v (1.18)	16.3
3	BP, GI, R, S	5-10	Yes	3	a (0.1)	22.3	a (11.7)	45.2
4	BP, R, S	5	Yes	2	v (0.01) p (0.01)	107	v (11.4) p (7.12) d (4.06)	21.5
5	BP, R, S	5-10	Yes	4	p (0.1)	88	p (0.77)	NA
6	BP, GI, R, S	10-15	Yes	3	p (0.001)	21.1	p (2.1)	NA
7	BP, R	5	Yes	1	v (0.01)	>5.000	v (>100) p (79.2) a (57.4)	26.5
8	BP, GI, R	10	Yes	3	a (0.001)	13	a (1.48)	24.6
9	BP, R	15-20	Yes	1	p (0.1)	714	p (9.73) v (0.61)	61.2
10	BP, GI, S	10	No	3	p (1)	42	p (1.73)	NA
11	BP, GI, S	20-30	Yes	1	p (0.1)	26	p (0.8) v (0.42)	NA
12	BP, S	20	Yes	3	v (0.1) p (1)	15.7	v (0.44) p (<0.35)	31
13	BP, S	NK	No	3	p (1)	66.1	p (0.54)	29.8
14	GI, R, S	5-10	No	1	a (0.1)	1649	a (23.1) v (4.88)	NA
15	BP, GI	10	Yes	3	v (1)	4.74	v (0.49)	NA
16	BP, GI, S	5	Yes	2	a (0.001)	155	a (6.2)	NA
17	BP, GI, R, S	30	Yes	18	v (0.001) p (0.01)	793	v (78.2) p (16.1) a (0.52)	24.4
18	BP, GI, S	5-10	Yes	70	p (1)	36	p (0.47) v (0.46)	32
19	BP, R	5	No	5	a (0.001)	20	a (10.7)	18.5
20	BP, S	5-10	Yes	5	p (0.1) v (1)	44	p (16.6) v (12.5)	NA
21	BP, GI, R	60-90	Yes	0.5	a,d,p,v (0.01)	17	NA	28

a, *Apis*; BP, reduced blood pressure documented by a medical professional; d, *Dolichovespula arenari*; GI, gastrointestinal symptoms (nausea, vomiting, diarrhea, abdominal pain); NA, not analyzed; NK, not known; p, *Polistes*; R, respiratory symptoms (dyspnea, wheeze-bronchospasm, stridor); S, involvement of skin-mucosal tissue (hives, pruritus, flushing, swollen lips/tongue/uvula); v, *Vespula*.

*Patients who referred feeling of impending doom after the sting.

†Time elapsed between anaphylaxis induced by Hymenoptera sting and performance of skin testing, total IgE and tryptase (expressed in months).

‡Skin tests were done for v,p,a in all the patients (end-point concentration expressed in μg/mL). Only positive results are presented in this table.

§Doses expressed in Phadebas RAST unit/mL.

||Specific IgE was performed for v,p,a in all the patients. Only positive results are presented in this table.

Evolution of analytical parameters through VIT

Serum total IgE, specific IgE to Hymenoptera, and BT were usually determined before VIT and in the subsequent annual visits. The median time of follow-up was 52 months (range, 2-250 months). Sixteen patients are still receiving VIT today. Whenever performed, the results of monitoring these parameters during VIT are summarized in Table IV.

Eighteen patients received more than 1 year of VIT. A statistical analysis with the first 5 determinations of specific IgE among these 18 patients was performed. When analyzing the data, values <0.35 kU/L were considered as 0.34 kU/L, and values >100 kU/L as 101 kU/L. Thus, the median value of specific IgE before VIT was 4.15 kU/L (range, 0.44-100). After 1 year of VIT, it decreased to 2.44 kU/L (range, 0.34-101), $P < .041$. After 2 years, the value decreased again to 1.12 kU/L (range, 0.34-101), $P < .002$. After 3 years, it decreased to 0.34 kU/L (range, 0.34-101), $P < .005$. After 4 years, although the median value

increased to 1.2 kU/L, the range was shortened (range, 0.34-69.4), so the decrease regarding the first determination was also significant, $P < .003$ (Fig 1; Table IV).

Among the 18 patients analyzed, in 9, specific IgE serum values decreased below 0.35 kU/L while undergoing VIT with a median time from the first determination of 26 months (range, 15-50 months). All 9 patients were receiving immunotherapy for wasp (6 for *Polistes*, 2 for *Vespula*, and 1 for mixed vespid venom and *Apis*) and had a baseline specific IgE <4.1 kU/L. All the other 9 patients presented baseline specific IgE levels >4.1 kU/L, with the specific IgE values remaining >0.35 kU/L after a median follow-up of 57 months (range, 4-250 months; $P < .0001$). In all cases in which Hymenoptera-specific IgE serum levels decreased below 0.35 kU/L, no further increase was observed throughout VIT, even in patients who were resting.

In 7 of 18 patients analyzed, specific IgE determinations to Hymenoptera different from the one they were receiving via

TABLE III. Clinical characteristics of patients during VIT

Patient no.	Immunotherapy	Premedication	VIT protocol		Adverse reaction during VIT	Re-sting	Symptoms after re-sting
			Initiation	Maintenance† (monthly)			
1	v	h1	Co	100‡	—	+	L
2	v	h1	Co	100	+ (S)	—	
3	a	h1	Co	100	—	—	
4	p	h1	Co	100‡	—	—	
	v	h1	Co	100‡	—	—	
5	p	h1	Co	100	—	+	L
6	p	h1	Co	100‡	—	+	L
7	v	h1	Co	100	—	—	
8	a	h1	Cl	100	—	—	
9	p	None	Cl	100	—	+	L
10	p	None	Co	100‡	—	+	L
11	p	None	Co	100‡	—	—	
12	v	h1	Cl	100	+ (BP, S)	+	S
13	p	None	Cl	100	—	+	L
14	a	h1	Co	100‡	—	+	L
15	v	None	Cl	100	—	+	L
16	a	h1	Co	100§	+ (BP, GI, S)	+	L
17	v	None	Cl	100	+ (BP, S)	—	
18	p	None	Co	100	—	—	
19	a	None* (h1,st,al)	Cl	100	+ (BP)	—	
20	p	None* (st)	Co	100	—	+	BP, CA, S
	v	None* (st)	Co	100			
21	mvv+a	h1	Co	300+100	+ (BP, R)	+	GI, R

a, *Apis mellifera*; al, antileukotrienes; BP, reduced blood pressure documented by a medical professional; CA, cardiac arrest; Cl, cluster; Co, conventional; GI, gastrointestinal symptoms (nausea, vomiting, diarrhea, abdominal pain); h1, antihistamines; L, local reaction (hives, pruritus and erythema); mvv, mixed venom vespid; p, *Polistes* spp; R, respiratory symptoms (dyspnea, wheeze-bronchospasm, stridor); S, involvement of skin-mucosal tissue (hives, pruritus, flushing, swollen lips/tongue/uvula); st, oral steroids; v, *Vespa* spp.

*Premedication initiated after adverse reaction (drug administered).

†Doses expressed in µg.

‡Interval of injection was elapsed over the second year of VIT.

§After 18 years of 50-µg maintenance doses, the patient tolerated an increase to 100-µg doses of Aquagen SQ extract.

immunotherapy were also performed. In all of them, specific IgE values also decreased from the first determination on ($P = .04$).

No significant differences were found in the annual determinations of serum total IgE and BT.

DISCUSSION

In this study, we report on the largest cohort of patients with SM undergoing VIT after an episode of anaphylaxis caused by Hymenoptera sting.

Association between HVA and mastocytosis has been previously described in patients with urticaria pigmentosa (UP),²⁶⁻²⁹ but few studies have included patients with SM with no skin involvement. Interestingly, most of our patients with SM had no cutaneous manifestations of the mastocytosis. In line with our findings, a monoclonal mast cell (MC) activation syndrome or clonal MC activation disorder has been recently described in patients with anaphylactic symptoms and clonal expansion of MCs in the BM,³⁰ without mastocytosis skin lesions.^{3,4} Monoclonal MC activation syndrome/MC activation disorder cases have also been associated with Hymenoptera anaphylaxis,^{3,4,6,31} as found in the current study.

In the normal population, anaphylactic reactions have been reported to be more common in males (2:1 ratio),^{1,32} as also found in our patient series, at a significantly higher (4:1) male:female ratio. Also consistent with the results reported in our environment, the prevalence of Hymenoptera sting was higher in wasps than in bees.^{33,34} Among wasps, the prevalence of anaphylaxis by paper

wasp seemed to be slightly higher than by yellow jacket wasp, which might differ from Central Europe.

Both BT and serum tryptase levels after HVA episodes have been traditionally considered useful parameters for the treatment of patients with anaphylaxis after Hymenoptera sting.^{9,35} In the current study, most patients did not show skin lesions, and thus there was a high percentage of patients in whom mastocytosis was suspected on the basis of an HVA episode associated with an increase in BT. In addition, in 2 of the patients who had skin lesions, HVA in association with increased BT levels was also the presenting symptom that led to the diagnosis of mastocytosis. However, it should be noted that normal BT values do not exclude the diagnosis of mastocytosis. Interestingly, in this study, patients with ISM in the absence of skin lesions had minor or no symptoms related to MC mediator release, and most of them were not on antimediator therapy, except after the Hymenoptera sting.

Adverse effects of immunotherapy to Hymenoptera venoms include large local and systemic reactions, anaphylaxis, and rarely, serum sickness.³⁶ Regarding patients with mastocytosis, the safety of VIT is controversial, with cases in which it is reported to be safe and effective,^{5,8-10} and fatal reactions.^{11,12} In the current study, 6 of 21 patients had an adverse reaction during VIT injection, and immunotherapy had to be discontinued in 2 of them. Among these 6 patients, 2 required a change in the VIT extract administered with good tolerance to the latter VIT extract. Altogether, these results indicate that despite no fatalities observed, VIT should be considered a risky procedure in patients

TABLE IV. Evolution of total IgE, specific IgE, and BT in patients throughout years undergoing VIT

Patient no.	IT	Total IgE (UI/mL)						Specific IgE (kU/L)						Baseline tryptase (ng/mL)						Duration† VIT
		B	1 y	2 y	3 y	4 y	last y	B	1 y	2 y	3 y	4 y	last y	B	1 y	2 y	3 y	4 y	last y	
1	v	104	210	119	82	110	74	v 17.5 p 10.5	4.8 3.4	4.33 2.92	2.44 1.63	3.2 1.97	1.74 1.29	29.1	30.9	22.8	17.9	13	13	Since 1999
2	v	81	—	—	—	—	—	v 1.18	—	—	—	—	—	16.3	—	—	—	—	—	Since 2007
3	a	22.3	11.2	9.21	—	—	—	a 11.7	3	1.12	—	—	—	45.2	46	48.2	—	—	—	Since 2005
4	v	107	NA	NA	170	216	300	v 11.4 p 7.12	15 2.94	5.58 1.09	6.68 1.16	4.38 0.98	3.64 1.27	21.5	21.5	NA	14.6	16.6	13.7	Since 2001
5	p	88	102.1	95.8	80.6	—	—	p 0.77	0.68	0.36	<0.35	—	—	NA	89.7	95.8	84.6	—	—	Since 2004
6	p	21.1	NA	NA	NA	9	10.5	p 2.1	0.53	<0.35	<0.35	<0.35	<0.35	NA	14.3	NA	NA	15.5	19.9	1998-2003
7	v	>5000	1319	693	423	274	234	v >100 p 79.2 a 57.4	>100 10.9 3.5	>100 5.96 2.16	>100 2.88 0.74	69.4 1.27 0.4	61.6 1.12 0.4	26.5	30.6	23	14.7	20.5	17.2	Since 2001
8	a	13	—	—	—	—	—	a 1.48	—	—	—	—	—	24.6	—	—	—	—	—	Since 2006
9	p	714	237	124	82.9	51.7	—	p 9.76 v 0.61	5.5 0.47	2.4 <0.35	1.09 <0.35	1.2 <0.35	—	61.2	76.4	71.5	87.2	70.9	—	Since 2002
10	p	42	52	24	27	16	27	p 1.73	2.44	0.6	<0.35	<0.35	<0.35	NA	NA	NA	41.4	32	36	2001-2007
11	p	26	118	80	22.6	26	24.5	p 0.82 v 0.4	1.36 <0.35	0.88 <0.35	<0.35 <0.35	<0.35 <0.35	<0.35	NA	NA	NA	38	22.9	15.3	2001-2006
12	v	15.7	4.93	5.84	—	—	—	v 0.44	<0.35	<0.35	—	—	—	31	25.6	39.1	—	—	—	2002-2004
13	p	66.1	NA	81	67	28.5	—	p 0.54	<0.35	<0.35	<0.35	<0.35	—	29.8	36.5	38.2	31.2	28	—	Since 2003
14	a	1649	NA	43	75	75	66.9	a 23.1 v 4.88	2.26 1.66	1.35 0.61	1.81 0.44	2.48 0.9	1.11 <0.35	NA	27.1	10.8	25	9	28.7	Since 1998
15	v	4.74	NA	NA	NA	4.99	5.5	v 0.49	NA	NA	NA	<0.35	<0.35	NA	NA	NA	NA	42.3	33.1	Since 2000
16	a	155	1	NA	22.4	14.2	143	a 6.2* v 78.2	3.5* 16.8	3.7* —	NA —	2.88 —	1.85 —	NA	NA	NA	11	14.6	18.7	Since 1989
17	v	793	483.3	—	—	—	—	p 16.1 a 0.52	4.64 <0.35	— —	— —	— —	—	24.4	26.3	—	—	—	—	Since 2005
18	p	36	23.2	NA	31.1	—	—	p 0.47 v 0.46	1.33 <0.35	NA NA	<0.35 <0.35	— —	—	32	34.5	NA	34.5	—	—	Since 2004
19	a	20	—	—	—	—	—	a 10.75	—	—	—	—	—	18.5	—	—	—	—	—	Since 2007
20	p	44	NA	11	NA	—	—	p 16.6 v 12.5	6.88 4.75	4.31 2.92	3.12 2.4	— —	—	NA	NA	47.7	NA	—	—	Since 2004
21	mvv+a	17	31	17	—	—	—	a NA v NA	0.36 <0.35	<0.35 <0.35	— —	— —	—	28	23	20	—	—	—	2004-2005

a, *Apis*; B, basal determination before initiation of VIT; mvv, mixed vespid venom; NA, not analyzed; p, *Polistes*; v, *vespula*.

In red, the specific-IgE of Hymenoptera venom to which the patient was not vaccinated.

*Doses expressed in Phadebas RAST unit/mL.

†Years undergoing VIT.

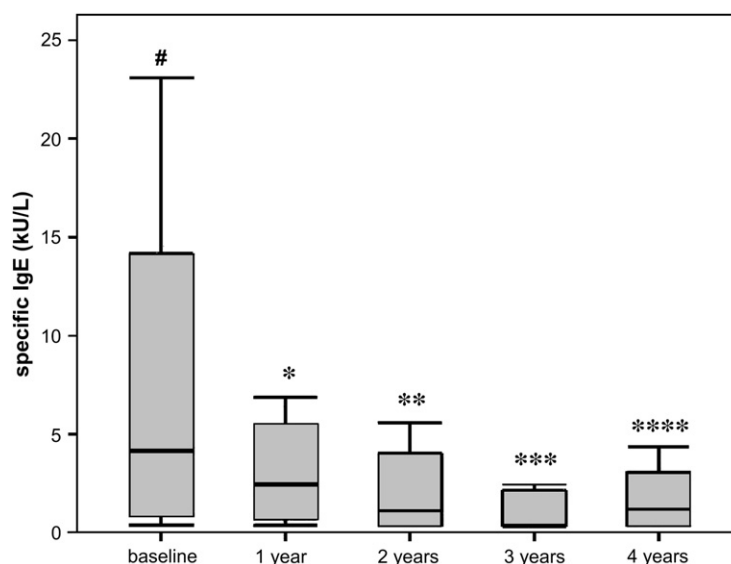


FIG 1. Evolution of specific-IgE values throughout the years undergoing VIT. Differences between baseline determination and following years: #versus * $P < .041$; #versus ** $P < .002$; #versus *** $P < .005$; #versus **** $P < .003$.

with mastocytosis and HVA. Therefore, specific cautions should be taken, including adequate premedication before VIT, at least during the initiation phase, and the availability of special conditions (eg, intensive care unit or a monitored setting with skill in the management of such an emergency) for the administration of the injections.

Usually, VIT is an effective treatment for individuals with systemic reactions, preventing morbidity and mortality from a subsequent systemic reaction in approximately 70% to 100% of the patients who receive it.⁷ In our study, 3 of 21 cases presented systemic reactions after a resting while undergoing VIT; 2 had relatively mild reactions, and 1 presented a severe systemic reaction. This patient was still at the initiation phase at the moment of the resting and was not stung again until the time of inclusion in the study, so the possibility of protection after receiving more doses remains unclear in this particular case. Interestingly, all 3 patients who experienced a systemic reaction after resting also had adverse systemic reactions during VIT. Because of small numbers, we cannot anticipate that a systemic reaction during VIT will predict a resting reaction. Despite this, VIT seems to be effective in patients with SM inducing protection against further stings, in line with previous reports.^{8,10}

In most patients without mastocytosis, VIT for 3 to 5 years induces long-term protection.⁵ It has been suggested that VIT could be safely discontinued in patients with detectable preimmunotherapy IgE antibodies whenever those antibodies disappeared during VIT.³⁷ Nevertheless, no further studies either are available to demonstrate the lower sensitivity of these patients after 5 years of immunotherapy^{5,38,39} or have determined the risk of discontinuation for patients with severe anaphylaxis. The residual risk of a systemic reaction to a sting after 5 years of immunotherapy is between 5% and 10%.^{7,37} During VIT, the levels of specific IgE to Hymenoptera in patients with mastocytosis experienced a significant decrease. Although specific IgE to Hymenoptera tends to decrease under detectable values after a median follow-up of 26 months, cases showing detectable amounts of Hymenoptera-specific IgE still showed a further decrease over that period. Traditionally, it has been proposed that patients with severe initial

reactions or near-death anaphylaxis might need immunotherapy for life. This idea, together with the results of this study, might support the convenience of extending VIT in patients with SM over standard duration,⁵ or even their lives. In addition, for patients presenting severe reactions, anti-IgE therapy might be recommended.⁴⁰

Cross-reactivity among components of different Hymenoptera species have been reported⁴¹ among Vespidae⁴² and also among bees and Vespidae.⁴³ Recent studies even support that immunotherapy against 1 species might be appropriate and sufficient in many cases of patients with multiple skin and/or serum positivities.⁴⁴ In our experience, in all patients sensitized to more than 1 Hymenoptera receiving immunotherapy for just 1 species, specific-IgE values for the different Hymenoptera species decreased.

Hymenoptera venom anaphylaxis has been reported in 20% of patients with mastocytosis in the absence of specific IgE, indicating that venom anaphylaxis can be triggered by non-IgE alternative pathways.^{1,8,29} In addition, IgE levels can be low in patients with mastocytosis and high MC burden. VIT should be prescribed to patients with IgE-mediated anaphylaxis, demonstrated by skin tests and/or specific serum IgE. There are no data to support a protective effect of VIT in patients with mastocytosis with anaphylaxis after Hymenoptera sting without specific IgE antibodies. *In vitro* studies to demonstrate the activation of MCs and/or basophils after exposure to Hymenoptera venom in these patients will help make these recommendations.

In summary, HVA in SM is a relatively common association. Life-threatening episodes, including death, can occur after Hymenoptera sting in patients with SM. VIT is an effective therapy in IgE-mediated HVA in SM. Its use is recommended despite a relatively high risk of adverse reactions during the build-up phase, because it provides protection from anaphylaxis in 75% of the patients.

Clinical implications: VIT is recommended in patients with SM.

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