

Venom Immunotherapy in Patients with Clonal Mast Cell Disorders: Efficacy, Safety, and Practical Considerations

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What is already known about this topic? Hymenoptera venom allergy and systemic mastocytosis are rare, and management of their association with immunotherapy is still a matter of debate.

What does this article add to our knowledge? We report herein a case series of 84 patients with mastocytosis and hymenoptera allergy who received immunotherapy. The treatment was overall well tolerated and achieved protection against stings in most patients.

How does this study impact current management guidelines? The results from this large case series should encourage and support the use of immunotherapy in patients with mastocytosis and hymenoptera allergy.

BACKGROUND: A preferential association between systemic mastocytosis (SM) and hymenoptera allergy (HVA) has been observed. Patients with both diseases are at risk for more severe reactions, and venom immunotherapy (VIT) may represent a life-saving treatment, but the use of VIT in such patients raised concerns about its safety.

OBJECTIVE: We evaluated a large population of patients with SM and HVA who received VIT.

METHODS: This prospective study was performed in Italy and Spain. A diagnosis of SM and HVA and a VIT prescription were made according to international recommendations. The patients were carefully followed up during VIT, with special attention to field stings.

RESULTS: A total of 84 patients (70 men, 14 women; mean age 52.1 years) were included, 81% with grade IV reaction, 91%

with indolent SM. No difference was seen between the Italian and Spanish patients. There were 10 adverse reactions during the induction phase: 3 with the conventional induction and 7 with the rush-modified induction, none resulted in epinephrine administration and/or hospitalization. Fifty patients had one or more field re-sting (95 episodes), none during induction. The time elapsed from starting VIT and first re-sting was 2 months to 7 years, and the number of re-stings per patient was 1-6. Of the 50 patients who were re-stung, 43 (86%) resulted in being fully protected. Seven patients had reactions, and the maintenance dose was safely increased to 200 mcg. The maintenance dose interval was not different between patients with and those without reactions at re-stings.

CONCLUSION: VIT is well tolerated, safe, and effective in patients with SM. © 2013 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol: In Practice 2013;1:474-8)

Key words: Systemic mastocytosis; Hymenoptera allergy; Venom immunotherapy; Safety; Efficacy

Systemic mastocytosis (SM) is a clonal disorder of the mast cell (MC) lineage, preferentially involving bone marrow (BM) and skin. SM is heterogenous and ranges from indolent types to aggressive ones. Recently, the term monoclonal MC activation syndrome (MMAS) has been proposed for those patients who do not fulfill SM criteria and could represent a different type of clonal MC disorders, although some of these patients might be in early stages of true SM with low MC burden.¹⁻⁵

Subjects with mastocytosis can experience symptoms due to a sudden and diffuse MC activation and the release of mediators (eg, generalized pruritus, abdominal pain, anaphylaxis). The diagnosis of SM requires, according to current guidelines, the presence of a major criterion (multifocal dense MC infiltrates in BM or in other extracutaneous organs) plus one minor criterion or at least 3 minor criteria. Minor criteria are abnormal morphology of extracutaneous MC (including BM smears), mutation in the *KIT* proto-oncogene at codon 816

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Abbreviations used

BM- Bone marrow
HVA- Hymenoptera venom allergy
Ig- Immunoglobulin
LLR- Large local reaction
MC- Mast cell
MMAS- Monoclonal mast cell activation syndrome
NS- Not significant
PCR- Polymerase chain reaction
RFLP- Restriction fragment length polymorphism
RT-PCR- Reverse transcriptase polymerase chain reaction
SM- Systemic mastocytosis
VIT- Venom immunotherapy

(D816V mutation) in an extracutaneous organ, expression of CD2 and/or CD25 on BM MCs, and an increased serum tryptase.⁶

In SM, MCs, which are increased in numbers and/or more prone to activation can respond with a sudden mediator release, either IgE mediated or not, with possible severe consequences. This is especially true in subjects with hymenoptera venom allergy (HVA) who are at higher risk of severe events than subjects without SM.^{7,8} From an epidemiologic point of view, there is a preferential association between SM and HVA,⁹ thus, patients with both diseases represent a special population that requires particular care in management. Venom immunotherapy (VIT) is recognized as a life-saving treatment for patients with HVA, but its use in SM raised controversies, especially due to safety concerns. When the problem was better addressed, the initial attitude was to avoid VIT in subjects with SM,^{10,11} although it was also suggested that VIT may also be safe and effective in patients with HVA and SM.¹²⁻¹⁴ Nonetheless, the observations so far provided involved small populations of patients, so that infrequent adverse events could have been missed and no well-supported recommendation could be made.

To better address this point and to provide more solid evidence, we prospectively followed up a relatively large number of patients with ascertained SM or MMAS and confirmed HVA who received VIT. Characteristics of patients, the safety of VIT, and the effectiveness of the treatment at field re-sting were carefully evaluated.

METHODS

This prospective observational study was performed at approximately the same time in Verona (Italy) and in Toledo (Spain), starting from year 2000 until now. A diagnosis of SM and HVA was made according to international recommendations^{1,3,15}; the prescription of VIT followed the European guidelines.¹⁶ Patient characteristics were recorded in a standardized database, and all the subjects were carefully followed up during the induction and maintenance phase of VIT, with a special attention to field re-stings. The diagnosis of SM in patients with a clinical suspicion and the use of VIT were considered part of the standard care, and no institutional review board approval, therefore, was required, although the ethics committees were notified of the study. All the patients signed an informed for privacy of data and diagnostic and/or therapeutic procedures consent as per routine practice.

Diagnosis

Patients with systemic reactions after Hymenoptera stings and with a serum tryptase level higher than 11.4 ng/mL (optimal cutoff level in normal subjects)¹⁷ or with urticaria pigmentosa, after informed consent, underwent BM examination to confirm or rule out SM or MMAS. The measurement of tryptase was performed not less than 2 weeks after the sting. According to international consensus, the diagnosis of SM or MMAS was based on BM aspirate, stained by May-Grünwald-Giemsa, and BM biopsy specimens were stained with an antitryptase mAb. The presence of atypical MCs on BM aspirate was investigated by using a specific 5-color mAb combination (CD25/CD2/CD45/CD34/CD117).^{3,18,19} In addition, the presence of mutation of exon 816 of the *KIT* gene in BM mononuclear cells was assessed in Italian patients by using RT-PCR with RFLP, followed by sequencing, and, in Spanish patients, in genomic DNA from fluorescence-activated cell-sorted BM MC by peptide nucleic acid-mediated PCR clamping followed by direct sequencing.^{20,21}

According to the presence of major and/or minor criteria in various combinations, the diagnosis of SM or MMAS was established. Concerning HVA, the standard diagnostic workup was carried out, including skin prick, intradermal test, and specific-IgE CAP-RAST (ThermoFisher, Uppsala, Sweden) assay.¹⁵ The severity of reactions at stings and during VIT were graded according to Muller.²² VIT was decided on the basis of the diagnostic results and clinical history. The diagnostic workup for mastocytosis and HVA was the same at the 2 centers in Italy and Spain.

Venom immunotherapy

Once the diagnosis of HVA was established, the patients received VIT according to 3 different induction (escalating dose phase) regimens: conventional, rush modified, and rush. The conventional protocol involved a 15-week induction phase with 1 dose/wk: 0.01, 0.1, 0.2, 0.4, 0.5, 1, 2, 4, 5, 10, 20, 40, 60, 80, and 100 mcg.²³ The rush-modified protocol involved the weekly administration of 4.11, 5, 10, 20, 40, 70, and 100 µg venom; the maintenance dose was reached in 7 weeks. In the rush induction, patients received increasing doses daily for 4 days (day 1: 0.01, 0.1, 1, and 2 mcg; day 2: 4, 8, 10, and 20 mcg; day 3: 40 and 60 mcg; day 4: 50 and 50 mcg).²² The achieved maintenance dose was then set at 100 mcg every 4-6 weeks. According to the established local procedures, extracts from different manufacturers were used, including the following: honeybee (Aquagen/Pharmalgen, Alk Abellò, Hornsholm, Denmark; Stallergenes, Antony Cedex, France), *Vespula* species (Pharmalgen, Alk Abellò; Stallergenes), and *Polistes* (Pharmalgen, Alk Abellò; Anallergo, Florence, Italy).

After the third year of treatment, the patients were proposed to continue with an extended maintenance administration (every 3 months). All the injections were given by a physician at the clinic, with resuscitation facilities immediately available. The patients were also prescribed autoinjectable epinephrine and rescue medications to be taken, if needed.

Evaluated parameters and follow-up

The safety of VIT was evaluated at each injection in a 30-minute observation period, and the possible late-onset reactions were assessed by detailed interviews at each visit. All reactions were recorded in the database. Reactions were graded as systemic (I-IV)²¹ or large local reactions (LLR). These latter are itching

TABLE I. Demographic, diagnostic, and clinical characteristics of the studied population, in total and subdivided by nationality

	Total population	Italian population	Spanish population	Italian vs Spanish, <i>P</i>
N	84	45	39	—
Mean age, y	52.1	54.1	49.8	NS
Age range, y	26-81	29-81	26-77	—
Men/women	70/14	37/8	33/6	NS
Diagnosis SM, no. (%)				
ISM + skin lesions	12 (14.3)	7 (15.5)	5 (12.8)	
ISM with no skin lesions	65 (77.4)	35 (77.8)	30 (77)	NS
MMAS	7 (8.3)	3 (6.7)	4 (10.2)	
Clinical symptoms or mediator effects, no. (%)*				
Peptic ulcer + bleeding	1 (1.2)	1 (2.2)	0	
Neurologic symptoms	4 (4.8)	3 (6.6)	1 (2.6)	NS
Diarrhea	4 (4.8)	2 (4.4)	2 (5.2)	
Osteoporosis	22 (26.2)	14 (31.1)	8 (20.5)	
Median (range) serum tryptase level, ng/mL	21.2 (6.7-103)	20 (9.9-103)	22.2 (6.7-40.6)	NS
Flow cytometry, no. (%)				
BM MC CD25+	80 (95)	42 (93.3)	38 (93.3)†	NS
BM MC CD2+	75 (89.2)	42 (93.3)	33 (84.6)†	
Exon 816 <i>KIT</i> mutation, no. (%)				
D816V	74 (88)	42 (93.3)‡	32 (82)‡	NS
D816H	2 (2.4)	1 (2.2)‡	1 (2.6)‡	
D816Y	1 (1.2)	0‡	1 (2.6)‡	
Reaction to first sting, no. (%)				
Grade I	1 (1.2)	1 (2.3)	0	
Grade II	7 (8.3)	3 (6.7)	4 (10)	NS
Grade III	8 (9.5)	0	8 (20)	
Grade IV	68 (81)	41 (91)	27 (70)	
Mean (SD) specific IgE, kU/L				
Honeybee	3.28 ± 9.26	1.85 ± 1.80	3.66 ± 10.28	NS
<i>Vespula</i> species	7.58 ± 2.61	2.56 ± 2.83	8.40 ± 2.13	NS
<i>Polistes dominulus</i>	4.69 ± 12.66	0.71 ± 0.67	5.33 ± 13.56	.05
Reactions with loss of consciousness, no. (%)	53 (63)	32 (71)	21 (53.8)	NS
VIT, no. (%)				
Honeybee	14 (16.6)	6 (13.3)	8 (20.5)	NS
<i>Vespula</i> species	30 (35.7)	21 (46.7)	9 (23.1)	.01
<i>Polistes dominulus</i>	31 (37)	18 (40)	13 (33.3)	.01
<i>Vespula</i> + <i>polistes</i>	9 (10.7)	— (0)	9 (23.1)	.001
Mean (SD) follow-up, y	7 ± 4	6 ± 3	7 ± 4	NS

BM, Bone marrow; ISM, indolent systemic mastocytosis; MC, mast cell; MMAS, monoclonal mast cell activation syndrome; NS, not significant; SM, systemic mastocytosis; VIT, venom immunotherapy.

*Present at diagnosis and requiring therapy.

†In 2 patients, the result of flow-cytometry CD2 analysis was not available.

‡In 6 patients, *KIT* mutation was not assessed because of the low number of cells obtained in the BM biopsy specimen.

reactions of edema and erythema with a diameter greater than 10 cm peaking at 24-48 hours.²⁴

All the patients were regularly followed up during the maintenance phase and instructed to immediately contact the physicians in the case of new stings. At re-stings, the severity of reaction, the use of rescue medications (including epinephrine), and the stinging insect (when recognized) were recorded. Specific IgE, IgG4, and serum tryptase were measured at baseline (before VIT), as per routine and after re-stings when feasible. IgE and IgG4 were assayed by an immunoenzymatic method (ImmunoCap; Phadia, Uppsala, Sweden) as well as serum tryptase (UniCap 100; Phadia). The Student *t*, Mann-Whitney *U*, and χ^2 tests were used for statistical analysis.

RESULTS

Patients

The total population of patients with confirmed SM or MMAS and HVA included 84 subjects (70 men; mean age, 52.1 years [range, 26-81 years]), as summarized in Table I. Of these patients, 81% had had grade IV reactions; of the aforementioned patients, 63% had ascertained loss of consciousness. Ninety-two percent of patients were diagnosed with indolent systemic mastocytosis, whereas the remaining had MMAS. When looking at the 2 populations (Italian and Spanish) separately, no relevant difference emerged concerning the demographic and clinical characteristics, except for the VIT prescription (Table I), which reflects the different distribution of Hymenoptera species in the 2 areas. In fact, the association of 2 VIT (*Vespula* and *Polistes*) was

TABLE II. Reactions during the induction phase

N	Sex	Age (y)	Protocol	VIT	Reaction
1	M	55	Rush modified	<i>Vespula</i>	LLR
2	M	60	Conventional	<i>Polistes</i>	LLR
3	F	37	Conventional	<i>Vespula</i>	LLR
4	F	53	Rush modified	<i>Vespula</i>	LLR
5	F	44	Rush modified	<i>Vespula</i>	LLR
6	M	74	Rush modified	Bee	LLR
7	M	55	Conventional	Bee	Grade I
8	M	59	Rush modified	Bee	Grade II
9	M	36	Rush modified	Bee	Grade II
10	M	76	Rush modified	<i>Vespula</i> + <i>polistes</i>	Grade III

LLR, Large local reaction; VIT, venom immunotherapy.

relatively more frequent in Spain. Also, there was an overall predominance of the male sex, probably because many patients were beekeepers, firemen, farmers, or gardeners (15 Spanish and 12 Italians).

Outcomes of VIT

Twenty-four patients received a conventional VIT (all in Spain), 57 received a rush-modified induction (43 in Italy and 14 in Spain) and 3 rush inductions (2 in Italy). VIT was overall well tolerated. There were 10 adverse reactions during the induction phases in 10 patients (12%) (6 LLR, 1 grade I, 2 grade II, and 1 grade III), all that occurred within 30 minutes (Table II). Thus, systemic reactions occurred only in 4 patients (4.7%). All those reactions were successfully treated with oral antihistamines, oral corticosteroids and/or inhaled bronchodilators, and epinephrine in the patient with the grade III reaction. After an adverse reaction, a slowing of the dose escalation was applied, and 2 patients (with LLR) also received premedication with oral antihistamines during the whole induction. No hospitalization was needed. Three reactions (2 LLR, 1 grade I) occurred with the conventional induction, whereas 7 episodes (4 LLR, 2 grade II, 1 grade III) occurred with the rush-modified protocol, but no significant difference was found between the 2 protocols (12.5% vs 12.3%, respectively; $P = .73$). No reaction was recorded during the rush induction, and no adverse effect was recorded during the maintenance phases. The duration of follow-up ranged between 2 and 11 years. Seven patients discontinued VIT during the maintenance period (4 spontaneously for moving away, 1 for myocardial stroke, 1 for acute leukemia, and 1 for acute renal failure) but none for VIT-related adverse events or field re-sting. Sixty of the 84 patients were on VIT for at least 5 years, and, after the first 5 years, the overall adherence (number of injections received/number of injections scheduled) was 88.4%.

During the maintenance phase, 50 patients (59.5%) had one or more field re-stings, for a total of 95 episodes, none during the induction. The stinging insect was clearly identified and described by these patients. The time elapsed from starting of the VIT and the first re-sting ranged from 2 months to 7 years, and the number of re-stings per patient ranged from 1 to 6. Of the 50 patients who had been re-stung, 7 had reactions (2 grade III and 5 grade IV), whereas the remaining 43 (86%) resulted in being fully protected (no reaction). The maintenance dose was increased to 200 mcg without adverse effects in the 7 patients with systemic reactions. Of them, 2 were re-stung with no reaction, whereas the remaining 5 were not re-stung so far. The general outcome of VIT in the population is summarized in Table III. The mean interval between maintenance doses was 6.7 ± 2.9 (mean $\pm$ SD) weeks in the Spanish group and 5.7 ± 1.2 weeks (mean $\pm$ SD) in the Italian group ($P = .13$). The maintenance-dose interval was not different between patients with and those without reactions at re-stings. No significant relationship emerged between the occurrence of adverse events and the extract used.

The baseline serum tryptase level was not different between the 10 patients who had reactions to VIT (either LLR or systemic) and the remaining ones (14.4 [range, 12.4-18.0] vs 16.2 [range, 13.4-21.3 ng/mL]; $P =$ not significant, Mann-Whitney U test), and this remained true for IgE and IgG4 (not shown). Also, no difference in specific IgE and IgG4 (not shown) was seen between baseline and after re-sting in the 17 patients whose serum was available (collected between 2 and 4 weeks after re-sting), whereas the tryptase levels significantly decreased (34.1 [range, 28.2-40.0 ng/mL] vs 22.2 [range, 15-36.1 ng/mL]; $P = .02$ Mann-Whitney U test).

DISCUSSION

SM is a rare condition, occurring in 3.4 of 100,000 in our surveys,²⁵ and it is quite frequently associated with HVA (and anaphylaxis) because it was reported that 11.1% of patients with severe HVA had SM (of the 13.9% patients with a tryptase level >11.4 ng/mL).⁹ Thus, this clinical setting should be managed by allergists in association with other specialists. The presence of HVA in subjects with SM represents an additional risk factor, because reactions are, overall, more severe and possibly life threatening. Because the association between HVA and SM is frequent, VIT represents a life-saving treatment, but a correct diagnosis and management of the disorder is mandatory. After some debate, mainly due to safety concerns, it is nowadays generally accepted that VIT should be prescribed to patients with SM and HVA.²⁶⁻²⁸ Nonetheless, this assumption derives from some small case series, so that infrequent adverse events could

TABLE III. Reactions (no. patients) in the total population before starting VIT and in patients who were re-stung before and during VIT

	Total population before VIT	No. of patients who were re-stung (before VIT)	No. of patients who were re-stung (during VIT)	χ^2 test (before vs during)
No reaction	0	0	43 (88 stings)	<.0001
Grade I	1	1	0	NS
Grade II	7	7	0	.01
Grade III	8	5	2 (2 stings)	.02
Grade IV	68	37	5 (5 stings)	<.001
Total	84	50	50	

NS, Not significant; VIT, venom immunotherapy.

not have been observed. Also, the efficacy of VIT in patients with SM has not been studied in large populations, and the most recent review included 75 patients from 8 different studies.²⁹

In joining together 2 homogeneous populations of patients, from Italy and Spain, we could achieve a relatively large number of cases with HVA and SM, so that more-robust recommendations can be provided for the use of VIT in such patients. Some of the cases were studied and described before,^{17,29} but, herein, we report a longer follow-up, a better detailed description, and a larger number of patients. VIT was well tolerated. A slightly higher number of adverse events were recorded with the rush-modified induction regimen but with no significant difference among protocols. Thus, despite not achieving statistical significance, it would be reasonable to suggest a less-aggressive induction in patients with SM. At variance with previous reports,^{26,29} none of our patients discontinued the treatment due to VIT-related adverse effects and no reaction was observed during the maintenance periods. Of note, also, the diagnostic procedures (skin prick and intradermal tests) were safe, as previously described for patients with SM.²⁷ Another relevant aspect is that VIT conferred full protection for the majority (86%) of patients who were re-stung, although this percentage is slightly smaller than that reported in patients without SM.³⁰⁻³² This also happens in those patients who receive an extended maintenance regimen, as repeatedly suggested.³³ However, although the number of sting reactions during VIT was strongly reduced, those reactions remained severe (grade III or IV). In those patients who were not fully protected at field re-stings, an increase of the maintenance dose to 200 mcg venom was safely carried out; thus, in such cases, an increase of the maintenance dose can be reasonably recommended.

In conclusion, based on the results of this large case series (when taking into account the rarity of the 2 conditions), patients with HVA and ascertained SM should receive the appropriate VIT. This treatment is not at higher risk and confers an effective protection against life-threatening systemic reactions.

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