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Effectiveness of Venom Immunotherapy: A Single-center Experience

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ABSTRACT

Introduction: Treatment outcomes in patients who completed or suddenly discontinued venom immunotherapy (VIT) are still uncertain.

Methods: A total of 71 patients who received conventional VIT were included in the study. Patients who experienced field stings were invited to the clinic, and allergic reactions were evaluated.

Results: The median age of the patients was 43 (35-54) years, and 70.4% (n=50) were male. Of the patients, 32 (45.1%), 29 (40.8%), and 10 (14.1%) received VIT with Vespula venom, Apis venom, and both Vespula and Apis venoms, respectively. Treatment was interrupted in 57 (80.2%) patients who could not access VIT due to drug unavailability. Thirty-eight (53.5%) patients experienced resting after initiation of VIT. Of the re-stung patients, 22 (57.8%) developed local reactions (LRs), and 16 (42.1%) developed systemic allergic reactions (SARs). All four patients who experienced anaphylaxis after re-sting were those whose treatment of VIT was incomplete. The VIT duration of patients with SARs was shorter than that of patients with LRs, although not significantly. SAR after the sting was significantly lower in patients with VIT duration >4 years. Thirty-three (46.5%) patients reported carrying adrenaline auto-injectors (AAIs), and 8 of them self-administered an AAI.

Conclusion: The effectiveness of VIT was correlated with its duration, and VIT lasting at least four years prevents SARs after field stings. The proportion of AAI carriers and the rate of self-administration were low among patients on VIT.

Keywords: Allergy, adrenaline auto-injector, hymenoptera venom, field sting, systemic allergic reaction, venom immunotherapy

Introduction

Stings by the order Hymenoptera, are common. Approximately 56.6%-94.5% of the general population is stung at least once during their lifetime (1). Bees from the Apidae and Vespidae families belong to this order. *Apis mellifera* (honeybee) of the Apidae family and *Vespula* spp. (wasp, yellow jacket) of the Vespidae family frequently cause allergic reactions (2). After a sting, Hymenoptera venom allergy (HVA) may be life-threatening (3). The onset of HVA cannot be predicted. A systemic allergic reaction (SAR) can occur after subsequent stings, even in those who did not experience a SAR during previous encounters (1). Sting symptoms vary from local reactions (LRs) at the sting site to SARs (4). Patients with HVA have a poor quality of life because even the course of mild systemic reactions cannot be predicted (2).

The incidence of anaphylaxis in sting-induced SAR is 0.6-42.8% (5). HVA ranks among the top three causes of anaphylaxis (6). The rate of recurrence of SAR following a subsequent sting in adults is 20%-70% (7). Hymenoptera venom-induced anaphylactic reaction is a clinical emergency. The patient must recognize this emergency and be informed regarding its acute management (8). The major treatment for Hymenoptera sting-induced anaphylaxis is intramuscular epinephrine. Delayed administration of epinephrine is a risk factor that may determine an unfavorable outcome of the acute anaphylactic episode. For patients with SAR, the teaching of appropriate techniques for self-administration of adrenaline and the prescription of an adrenaline auto-injector (AAI) are necessary to prevent future anaphylaxis (6).

The only protective treatment for systemic reaction following Hymenoptera sting is venom immunotherapy (VIT). VIT is indicated for patients who are determined to have a history of sting-induced systemic reaction and to have sensitivity to venom of the liable insect by skin prick testing responses and/or serum specific IgE (sIgE) tests and/or basophil

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activation tests When the first sting reaction is severe and allergy testing is similarly positive for *Vespula* and *Apis* venoms, VIT using both venoms should be considered (4). VIT provides protection against SAR in 77%-84% of honeybee stings and 91%-96% of vespid stings (5). Following discontinuation of the treatment, a long-term effect is observed. There is no biomarker of the response to allergen immunotherapy to aid decision-making regarding VIT continuation or discontinuation (9). Life-long treatment should be considered in patients who experience SARs or systemic side effects during VIT, and in patients with honeybee venom allergy and a high risk of future honeybee stings (4).

Allergen immunotherapy can alter the natural course of allergic diseases by reducing medication use and providing long-lasting symptomatic control. Indeed, it is the only potentially curative treatment (9). It not only ameliorates the disease by reducing the number of reactions, but also improves the psychological quality of life (10). Some of the patients started on VIT could not complete their treatment due to drug supply disruptions in Türkiye. We retrospectively analyzed the sting reactions of all patients during and after VIT, as well as the proportion of AAI carriers among these patients.

Methods

Study Design

The study was approved by the Non-Drug and Medical Device Research Ethics Committee of Necmettin Erbakan University (approval number: 2024/4852, date: 15.03.2024). A total of 83 patients who received VIT in the Adult Immunology and Allergy Department between January 2016 and April 2022 were reviewed. The demographic characteristics, clinical histories, and laboratory results of the patients were retrieved from their medical records and electronic health records. All patients who had initiated VIT at the hospital were contacted by phone; 12 patients who could not be reached were excluded from the study. Patients who did not complete their treatment were invited for a follow-up visit. Informed written consent were obtained from all participants.

Venom Immunotherapy

VIT was initiated using Alutard SQ allergen extract (ALK-Abelló, Denmark) for patients with honeybee and wasp venom allergy. Doses were administered under physician supervision in an equipped treatment room. The injections were performed according to the conventional protocol with weekly increasing doses and a 15-week up-dosing scheme. During the maintenance phase, which was reached within about 16 weeks, the interval between the injections was gradually increased. The standard maximal maintenance dose of 100,000 U-SQ/mL was reached. Maintenance treatment was planned to last >5 years in all patients. Patients with VIT ≥5 years were considered to have completed treatment. However, due to the poor availability of immunotherapy in Türkiye for the last 2 years, VIT was discontinued in patients.

Venom-Specific IgE Antibodies

Allergy was diagnosed based on a conclusive history and a corresponding venom sensitization (sIgE) in serum. Before beginning VIT, basal serum tryptase (sBT) and sIgE antibodies against *Apis* and *Vespula* venoms were assayed. The plasma sIgE titers were measured using the Phadia Unicap 100 instrument (Thermo Fisher Scientific, Waltham, MA) and the Immuno-CAP system by fluoroenzyme immunoassay. The results are expressed as kilounits per liter. An *Apis* and/or *Vespula* sIgE level of ≥ 0.35 kU/L was considered indicative of positivity.

Severity of Reactions

Patients experiencing stings were in the maintenance phase. Allergic reactions following re-sting were graded by severity. A mild SAR was defined as cutaneous symptoms including itching, urticaria, erythema, and mild angioedema. A moderate SAR was defined as transient symptoms of hypotension, dyspnea, abdominal pain, vomiting, dizziness, and vertigo. A severe SAR was defined as anaphylaxis, hypotension, loss of consciousness, and asthma-induced and laryngeal edema-induced dyspnea (11).

Statistical Analysis

Data entry and statistical analysis were performed using the SPSS statistical package (v. 22.0; SPSS Inc. Chicago, IL). Continuous variables are expressed as medians and interquartile ranges, and categorical variables as numbers and percentages. Comparison of non-normally distributed numerical data with categorical data was performed using the Mann-Whitney U test. For comparison of categorical data, Pearson's chi-squared test and Fisher's exact test were used. A value of $p<0.05$ was considered indicative of statistical significance.

Results

Demographic and Clinical Characteristics

Seventy-one patients who had SARs following a Hymenoptera sting, confirmed sensitivity, and who received VIT, were included in the study. sIgE against the responsible insect confirmed the patients' venom allergy. The median age of the patients was 43 (35-54) years, and 50 (70.4%) were male. All 11 beekeepers (15.5%) were male. Of the patients, 29 (40.8%) received VIT using *Apis* venom and 32 (45.1%) received VIT using *Vespula* venom, respectively. Ten patients (14.1%) reported allergic reactions after both *Apis* and *Vespula* stings. These patients, who were found to be sensitized to both venoms, received VIT using both venoms. Patients received VIT for an average of 42 (9-53) months. Of the patients, 14 (19.7%) completed VIT (VIT ≥5 years); 57 (80.2%) did not complete 5 years of VIT because of the poor availability of VIT in Türkiye (Table 1).

Reactions due to Accidental Field Re-Stings

After initiation of VIT, 38 (53.5%) patients experienced stings. Of the 38 patients who experienced stings, only 8 received VIT for ≥5 years, while 30 were patients who had discontinued VIT. Among them, 18 (47.3%) experienced field stings during VIT, and 20 (52.6%) after VIT was discontinued (Figure 1). Of the patients, 21 and 17 reported *Apis* and *Vespula* re-stings, respectively. Two patients re-stung by a bee other than the one for which VIT was administered, developed LRs. Of the re-stung patients, 22 (57.8%) developed LRs and 16 (42.1%) developed SARs. The four patients who developed severe SARs had symptoms of anaphylaxis (Table 2).

Table 1. Demographic, clinical and immunotherapy parameters

Variables		Data
Total number of patients		71
Age (median-IQR)		43.0 (35.0-54.0)
Gender, n (%)	Female	21 (29.6)
	Male	50 (70.4)
Venom immunotherapy, n (%)	Apis VIT	29 (40.8)
	Vespula VIT	32 (45.1)
	Double VIT	10 (14.1)
Occupation, n (%)	Beekeeping	11 (15.5)
	Others	60 (84.5)
Duration of VIT, month (median-IQR)		42.0 (8.0-53.0)
Duration of VIT, n (%)	<1 year 1 to 3 years >3 years Completed VIT	20 (28.2) 14 (19.7) 23 (32.4) 14 (19.7)

VIT: Venom immunotherapy, IQR: Interquartile range

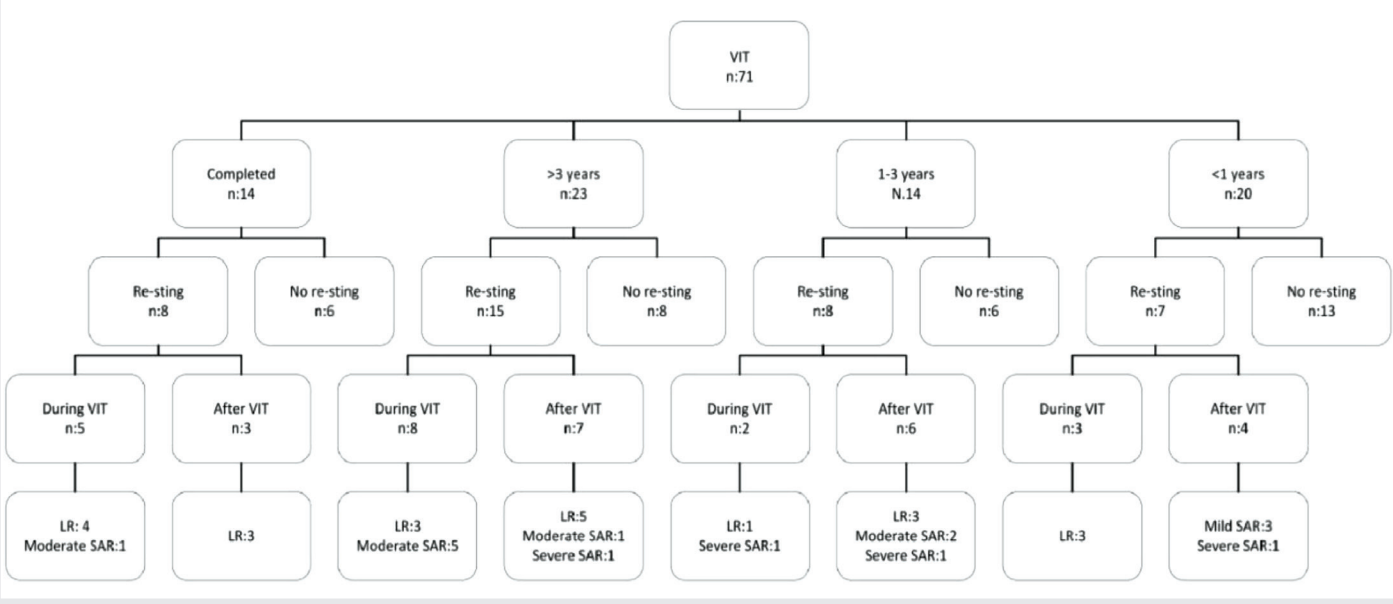

Figure 1. Patients reacting to field re-sting during or after VIT by duration of VIT
VIT: Venom immunotherapy, LR: Local reaction, SAR: Systemic allergic reaction

Of the re-stung patients with a VIT duration <1 year, three developed LRs and four developed SARs, of which three were mild and one was anaphylaxis. Of the re-stung patients with a VIT duration of 1-3 years, four developed LRs and four developed SARs (two moderate and two cases of anaphylaxis). Of the re-stung patients with a VIT duration >3 years, eight developed LRs and seven developed SARs, six moderate and one anaphylaxis. Of the re-stung patients who completed VIT, seven developed LRs and one developed moderate SARs. Figure 1 shows, in detail, the timing of patient stings and their reactions in relation to the duration of VIT.

Competence with the AAI

Of the patients, 33 (46.5%) reported that they carried AAIs, and 38 (53.5%) reported that they did not. In addition, 20 of 38 re-sting patients had AAI. Of the 20 patients carrying AAI who were re-stung, 8 self-administered AAI, while 12 did not. Six of the eight patients who self-administered AAIs were admitted to an emergency department (ED) (Table 2). Of the patients who self-administered AAIs, three did so before symptom onset and five had SAR symptoms. Three of the five patients who had SARs and self-administered AAIs developed anaphylaxis. Four patients with anaphylaxis were admitted to an ED, three of whom self-administered AAIs. Six of eleven beekeepers carried AAIs.

Comparison of Types of Reaction Observed in Bee-Stung Patients and Their Demographic and Immunotherapy Characteristics

The median age of patients who experienced SARs after re-sting was 42 years, compared to 51.5 years for those who experienced LRs (p=0.042). The gender distribution, occupations, and AAI self-administration

status were similar between the patients who experienced SARs and LRs (p>0.05). The median time of administration was 39 months and 50 months in patients with SARs and LRs, respectively (p=0.052). The type of reaction did not differ between patients with VIT durations of >3 years and ≤3 years (p=0.258). However, the type of reaction differed between patients with VIT duration of >4 years and ≤4 years (p=0.037) of 11 beekeepers, 10 were re-stung (Table 3).

Discussion

VIT is the only curative modality for HVA. It requires injections every 4-8 weeks and must be continued for 3-5 years, making it costly. We evaluated reactions after field re-sting in patients who started but did not complete VIT due to the unavailability of VIT in Türkiye and in patients who received VIT for ≥5 years in Türkiye. Of the 71 patients receiving VIT, 38 experienced accidental field re-sting during or after VIT. Among them, 16 reported SARs. The VIT duration of the patients

Table 2. Identified insects and results of field stings

Variables		Data
Field re-sting, n (%)	Yes No	38 (53.5) 33 (46.5)
Stinging bee species	Apis Vespula	21 17
Number of field stings, n	Without allergic reactions With allergic reactions Mild SAR Moderate SAR Severe SAR	22 16 4 8 4
Carrying AAI, n(%)	Yes No	33 (46.5) 38 (53.5)
Carrying of AAI, n	Yes Using AAI AAI alone AAI + hospital visit Not using AAI Hospital visit No	33 8 2 6 12 6 38

SAR: Systemic allergic reaction, AAI: Adrenaline auto-injector

Table 3. Comparison of types of reactions in patients re-stung after immunotherapy and their demographic, clinical and immunotherapy characteristics

Characteristics SAR (n=16)		Patients re-stung after initiation of immunotherapy (n=38)		p
		LR (n=22)		
Age (median-IQR)		42.0 (30.7-52.7)	51.5 (38.5-58.0)	**0.042**[a]
Gender, n (%)	Female	6 (37.5)	4 (18.2)	0.168[b]
	Male	10 (62.5)	18 (81.8)	
Occupation, n (%)	Beekeeping	5 (31.3)	5 (22.7)	0.411[b]
	Others	11 (68.8)	17 (77.3)	
VIT, n (%)	Apis	8 (50.0)	10 (45.5)	-
	Vespula	5 (31.3)	9 (40.9)	
	Double VIT	3 (18.8)	3 (13.6)	
Using AAI, n (%)	Yes	5 (31.3)	3 (13.6)	0.181[b]
	No	11 (68.8)	19 (86.4)	
Duration of VIT, month (median-IQR)		39.0 (9.7-47.2)	50.0 (36.0-60.0)	0.052[a]
Duration of VIT n (%)	≤3 years	8 (50.0)	7 (31.8)	0.258[c]
	>3 years	8 (50.0)	15 (68.2)	
Duration of VIT n(%)	≤4 years	12 (75,0)	9 (40,9)	**0.037**[c]
	>4 years	4 (25.0)	13 (59.1)	

[a]: Mann-Whitney U test; [b]: Fisher's exact test; [c]: Pearson's chi-squared test
VIT: Venom immunotherapy, LR: Local reaction, SAR: Systemic allergic reaction, IQR: Interquartile range

who experienced SAR was shorter than that of those who experienced LRs, although not significantly. SAR after sting was also lower in patients with VIT duration >4 years (p=0.037). Thus, >4 years of VIT protected patients from SAR. All four patients with severe SAR who reported symptoms of anaphylaxis had their VIT discontinued. Of the patients who completed VIT, seven developed LRs and one developed SARs, after re-sting. The awareness of patients receiving VIT of carrying and self-administering AAI was poor; only 33 of the patients receiving VIT, were carrying an AAI. Among the 20 re-stung patients carrying an AAI, only 8 self-administered AAI.

In a previous study in Türkiye, 29% of the general population was sensitized to Hymenoptera venom. Hymenoptera stings and allergies are typically caused by honey bees (*A. mellifera*) and wasps (*Vespula* vulgaris) (12). In this study, rates of VIT using *Apis* (40.8%) and *Vespula* (45.1%) venom were similar. Component-resolved testing was not available in our clinic to eliminate cross-reactivity in patients susceptible to both venoms. Among the patients with sensitization to both venoms, 10 patients (14.1%) with a history of reaction to both *Apis* and *Vespula* stings underwent VIT with both venoms. When the causative insect was identified, we administered VIT using only the causative species, even in the presence of determined sensitivity to both bee species.

The incidence of allergy to Hymenoptera stings is higher among males (13). In our study, 50 (70.4%) of the patients receiving VIT were male. Field re-sting was more common in male patients than in female patients (28/10). The increased risk of re-sting, might be because of the larger number of male patients than female patients. In this study, 11 beekeepers (15.5%) were males. All 11 beekeepers received VIT using *Apis* venom; 10 experienced re-stings. The rate of SAR after re-stings among beekeepers is reportedly 14%-38%, which is higher than in the general population (14). In this study, among 10 re-stung beekeepers, 4 had LRs, 2 had mild SARs, and 1 had a severe SAR.

SARs following accidental Hymenoptera stings have been reported, even in individuals with negative sensitivity tests after VIT (15). Evaluating the effectiveness of VIT is thus challenging. A sting challenge test, involving an insect to which a patient is allergic to sting, is the gold standard for demonstrating the effectiveness of VIT (4). When this test cannot be performed, the results of natural field sting reactions may be beneficial for evaluating the effectiveness of VIT. While accidental field stings were recorded in some studies, intentional sting challenges were recorded in hospital settings in others (15). In this study, 38 patients (53.5%) experienced re-sting after initiation of VIT. The likelihood of field sting was similar to previous reports (50% to 62%) (16,17).

The risk of SAR after re-sting is higher in individuals with *Apis* venom allergy (18). Furthermore, the effectiveness of VIT for *Apis* venom is lower than for *Vespula* venom. The rate of recurrence after discontinuation of VIT is 7.5% for *Vespula* and 15.8% for *Apis* (19). In this study, 62.5% of SARs involved *Apis* after accidental field re-sting, possibly because 55% of the re-stung patients (21/38) reported re-stings with *Apis*, or because A. mellifera injects a large quantity of venom (5). Similarly, we observed that re-sting reactions to *Apis* were more dangerous than those to *Vespula*.

HVA-induced anaphylaxis is associated with increased sBT and mastocytosis in 5% of cases (20). However, we found neither increased sBT levels nor mastocytosis in our patients. Thus, mastocytosis, a factor known to cause VIT treatment failure, was not found in this study.

The rate of SAR after re-sting was 60% in untreated patients, while it was 5% in those on VIT. The rate of recurrence of SAR after discontinuation of VIT is 10%-15% higher in patients treated for <5 years (21). In this study, 16 of 38 patients who experienced field re-stings (42%) developed SARs. The high rate of SARs is likely attributed to not all the patients having received VIT for a sufficient duration, which is a determinant of its long-term effectiveness. In this study, the VIT duration was not significantly different among patients who developed LRs after field re-sting compared to those who experienced SARs. SARs occurred in 8 of 15 re-stung patients who had received VIT for ≤3 years, and 3 of the 8 SARs were anaphylaxis. Immunotherapy was highly effective in a previous study, with a 3% incidence of sting-related reactions after four years of VIT (22). In this study, among re-stung patients, SAR developed more significantly in those with VIT <4 years. None of the re-stung patients who completed VIT developed anaphylaxis. Because of the residual risk of SAR, patients are advised to take precautions against Hymenoptera stings and to carry AAIs, including those on VIT (23).

AAIs are infrequently used by patients of all ages to treat anaphylaxis (24). In a Japanese study, 30%-50% of outdoor workers and 30% of beekeepers with a history of SARs after Hymenoptera stings were carrying AAIs (25). In this study, 33 (47%) of the patients were carrying AAIs. Of 11 beekeepers, 6 (55%) were carrying AAIs. The most common reason for not carrying AAIs was that they had expired and were not prescribed again. Another reason was the inconvenience of carrying AAIs, resulting from their large size. Among individuals with a history of anaphylaxis, the rate of self-administration of AAI was 27% (26). In this study, 8 of 20 re-stung patients (40%) who were carrying AAIs self-administered AAIs. The most common cause of non-use of AAI was confusion about its timing. The mortality rate increases if adrenaline injection is delayed by more than 30 minutes after the occurrence of an SAR following a Hymenoptera sting. Appropriate use of AAI is important (25).

Study Limitations

One limitation of the study is the small patient population. Therefore, the results are not fully generalizable. Another issue is the large number of patients who failed to complete treatment due to the abrupt discontinuation of VIT supply in Türkiye. Thus, evaluating the effectiveness of VIT became complicated because the duration of VIT was extremely variable among the patients. Since the supply of VIT has not been established in our country, treatment has not yet been restarted for patients with incomplete therapy. Another limitation of this study is that we were unable to study biomarkers of susceptibility other than sIgE (e.g., component-based testing) and therefore could not include these parameters in our analysis. We also believe that a detailed evaluation of clinical symptoms, is crucial for the diagnosis and differentiation of HVA.

Conclusion

Our objective in this study was to determine the reactions after accidental field stings in the patients receiving VIT, particularly in patients whose treatment was aborted due to poor availability of VIT in Türkiye. The incidence of SAR after field re-sting was higher in patients whose VIT was discontinued. The patients who experienced anaphylaxis after re-sting failed to complete VIT or received VIT for a short period. Our results strongly suggest that the effectiveness of VIT mainly depends on the duration of treatment. In patients who discontinue VIT after 3 to 4 years, it would be useful to prospectively evaluate recurrent systemic sting reactions with sting challenge test. Another important aspect of this study is the demonstration of lower rates of carrying and self-administration of AAI among patients receiving VIT. The fact that some patients experienced anaphylaxis after re-sting despite being on VIT suggests the importance of carrying an AAI.

Ethics

Ethics Committee Approval: The study was approved by the Non-Drug and Medical Device Research Ethics Committee of Necmettin Erbakan University (approval number: 2024/4852, date: 15.03.2024).

Informed Consent: Informed written consent were obtained from all participants.

Footnotes

Authorship Contributions: Concept - F.A.A., F.Ç., T.Ö., R.E., S.A.; Design - F.A.A., F.Ç., S.A.; Data Collection or Processing - F.A.A., T.Ö., M.K., F.S.A., M.E.G.; Analysis or Interpretation - F.A.A., F.Ç., R.E., F.S.A., M.E.G., S.A.; Literature Search - F.A.A., M.K., F.S.A., M.E.G.; Writing - F.A.A., T.Ö., M.K., M.E.G., S.A.

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