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Original Research

Venom Immunotherapy in Patients: Clinical Characteristics, Treatment Outcomes, and Real-Life Safety Data

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Abstract

Objectives: Venom-specific immunotherapy is recognized as the gold standard treatment for honey bee and wasp venom allergies. This study aims to evaluate the clinical characteristics and treatment outcomes of patients diagnosed with honey bee and wasp venom allergies who commenced immunotherapy.

Methods: This study encompasses data from 43 patients who presented with honey bee and wasp venom allergies at Ondokuz Mayis University and initiated venom immunotherapy (VIT). We retrospectively examined the patients' demographic characteristics, history of atopic diseases, allergy history, characteristics of honey bee and wasp venom stings, severity of reactions, laboratory values, administered treatments, and side effects.

Results: Among the 43 patients included in our study, 9 (20.9%) were female, and 34 (79.1%) were male. A history of atopic disease was present in 34.8% of the patients, and a family history in 51.1%. The severity of systemic reactions was evaluated according to Müller's classification, with grade 4 reactions being the most frequent (48.8%). Of the 43 patients who received VIT, 28 (65.1%) were treated for *Apis mellifera*, 9 (20.9%) for *Vespula vulgaris*, and 6 (14%) for both species. Twelve patients experienced side effects during VIT, leading to discontinuation in two cases due to patients' reluctance to continue. The remaining 22 patients, who were stung again during or after completing VIT, experienced milder systemic reactions.

Conclusion: This study delineates the demographic and clinical characteristics of patients with honey bee and wasp venom allergies, highlighting the efficacy of VIT treatment. Despite the occurrence of side effects related to VIT, both previous studies and our findings suggest that these side effects are not more severe than systemic reactions resulting from stings. The absence of severe systemic reactions in patients who were stung again during or after receiving VIT underscores the effectiveness of the immunotherapy.

Keywords: Anaphylaxis, atopic diseases, honey bee allergy, hymenoptera stings, systemic reactions, venom immunotherapy, wasp venom allergy

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Bee allergy is defined as a classical IgE-mediated (Type I hypersensitivity reaction) allergic disease.[1] In the community, 56-94% of individuals have encountered hymenoptera (bees, wasps, hornets, etc.) stings at least once in their lives.[2] Studies have indicated that serious systemic reactions related to stings occur in adults at a rate of 1.2-4.3%, in children at 0.2%, and in beekeepers at 6.5%.[3]

Venom immunotherapy (VIT) is considered the gold standard treatment aimed at reducing the risk of systemic reactions in individuals with hymenoptera venom allergy. VIT

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provides desensitization to the venom to which the patient is sensitive. This treatment protocol is accomplished by gradually increasing venom doses administered subcutaneously. Successfully applying VIT is an effective method for preventing secondary anaphylactic reactions to bee stings. VIT reduces the risk of recurrent life-threatening reactions from 30-60% to below 5% in most patients.[4] Protection against recurrent anaphylactic reactions is often achieved within one week after reaching maintenance doses.[5] Therefore, VIT should be administered to these children. Beyond access to epinephrine and avoidance of hymenoptera, VIT has been shown to significantly improve health-related quality of life.[6]

Methods

Patient Selection and Data Collection

A total of 77 patients with allergic reactions due to bee stings presented to the Department of Pediatrics, Division of Allergy and Immunology, Ondokuz Mayis University Faculty of Medicine in Samsun. Among them, 43 patients who underwent immunotherapy were included in the study (Fig. 1). Patient files were retrospectively reviewed to obtain information about the patients' medical history, clinical features, and treatment processes. Patients with incomplete information were contacted to complete missing data. The patients' atopic history, family history of beekeeping, type of bee causing the sting, site of sting, month of sting, and clinical symptoms after the sting were recorded. Additionally, the patients' conditions before, during, and after VIT were evaluated.

To determine the severity of reactions (Fig. 2), the Muller classification was used:

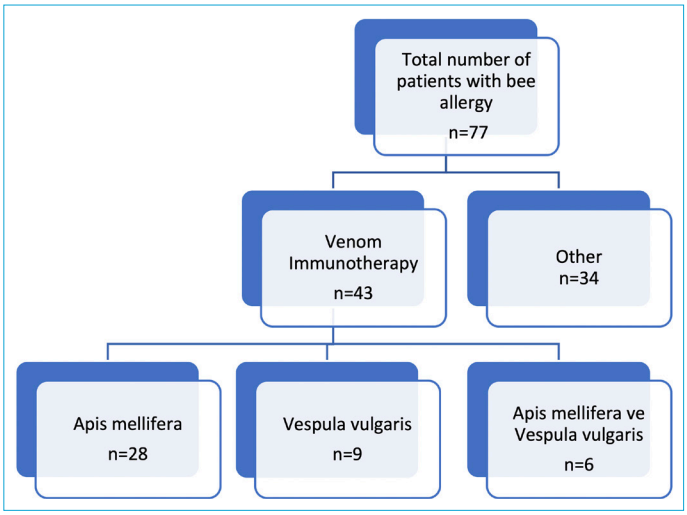

Figure 1. The distribution of patients with Apis mellifera and Vespula vulgaris allergies who have started treatment.

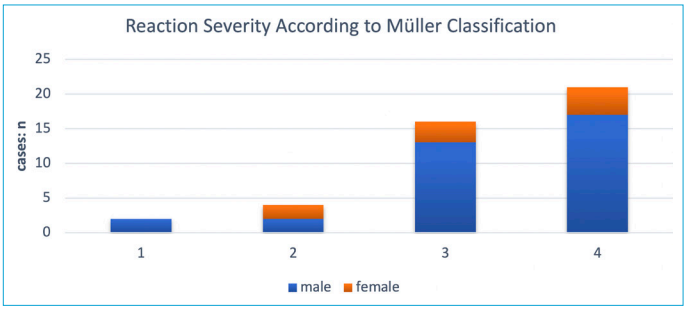

Figure 2. Reaction severity according to Müller classification.

Grade 1: Generalized urticaria, itching, malaise, and anxiety.

Grade 2: In addition to Grade 1 symptoms: angioedema, chest tightness, nausea-vomiting, abdominal pain, diarrhea, dizziness.

Grade 3: In addition to the above: dyspnea, wheezing, stridor, dysarthria, hoarseness, confusion.

Grade 4: In addition to the above: hypotension, collapse, loss of consciousness, incontinence, cyanosis.

Laboratory Evaluation

Skin Prick Test and Specific IgE Test (spIgE)

Standardized purified venom antigens of *Apis mellifera* and *Vespula vulgaris* (manufactured by ALK–Abello, Horsholm, Denmark) were utilized for skin tests. Intradermal skin testing was conducted on the ventral surface of the forearm using increasing concentrations (0.0001, 0.001, 0.01, and 0.1 mg/mL), along with positive (histamine dihydrochloride) and negative controls. Positive test results were determined based on the guidelines of the European Academy of Allergy and Clinical Immunology, with intradermal test results considered positive if the difference from the negative control exceeded 3 mm.

The levels of allergen-specific IgE in serum samples were assessed using the ImmunoCAP 1000 system by Phadia (Sweden). Each serum sample was tested for IgE levels against Honey Bee (*Apis mellifera*, I1) and Wasp (Vespula Spp, I3) using the ImmunoCAP test kit designated for the Bee Venom Components IgE panel (test code: 6759). Allergen-specific IgE levels were categorized according to a predetermined evaluation scale, with values below 0.10 kU/L considered negative and values above 0.10 kU/L considered positive. Considering the potential for cross-reactivity, the diagnosis was based on clinical history, prick test, and serum-specific IgE results; component-resolved diagnostics were not performed due to cost constraints.

Statistical Analysis

The data analyses were conducted using SPSS (Statistical Package for Social Sciences) 23 (SPSS Inc., Chicago, IL, USA)

and AMOS (Analysis of Moment Structures) 26 programs. Descriptive statistics included counts and percentages for categorical variables, while mean, standard deviation, minimum, maximum, and median values were calculated for numerical variables. The comparison of proportions in independent groups was conducted using the Chi-square analysis. As the comparisons of numerical variables did not meet the assumption of normal distribution, the comparison between independent groups was carried out using the Mann-Whitney U test.

A statistical significance level of $p<0.05$ was considered as the threshold for statistical significance.

This study obtained approval from the local ethics committee of Ondokuz Mayis University (Number/Date: 2022000001-1/04.03.2022). Patients' informed consent was obtained. Our study was conducted in accordance with the Helsinki Declaration.

Results

Demographic Information

A total of 43 patients were included in the study for immunotherapy. Of these, 79.1% were male and 20.9% were female. Regarding age distribution, 14% of the patients were below 10 years old, 55.8% were between 10-20 years old, and 30.2% were above 20 years old. In terms of geographic distribution, 55.8% of the patients were from Ordu, 30.2% from Samsun, and the remaining 14% were from the Amasya, Tokat, and Sinop regions. These patients presented to our clinic for evaluation, and following necessary examinations, VIT was promptly initiated.

Atopic Disease History

In evaluating the allergic disease history of a total of 43 patients, 21 patients (41.2%) had no history of allergic diseases. Among those with a history of allergic diseases, 9 patients (17.6%) had asthma, 8 (15.7%) had bee venom allergy, 4 (7.8%) had drug allergy, 4 (7.8%) had food allergy, 3 (5.9%) had allergic rhinitis, 1 (2.0%) had atopic dermatitis, and 1 (2.0%) had urticaria. These findings provide a detailed overview of the distribution of allergic diseases within the patient group (Table 1).

Table 1. Demographic and clinical characteristics of patients undergoing venom immunotherapy

	n=43	% percentage
Family History of Atopic Diseases		
None	21	41.2
Asthma	9	17.6
Bee Venom Allergy	8	15.7
Drug Allergy	4	7.8
Food Allergy	4	7.8
Allergic Rhinitis	3	5.9
Atopic Dermatitis	1	2.0
Urticaria	1	2.0
Allergic Reaction-Causing Bee Species		
Apis mellifera	28	65.1
Vespula vulgaris	9	20.9
Both	6	14.0
Bee Sting Season		
Summer	26	60.5
Autumn	8	18.6
Spring	2	4.7
Winter	7	16.3
Bee Sting-Related Symptoms		
Local swelling	25	27.4
Difficulty breathing	23	25.2
Hypotension	17	18.6
Rash	9	9.8
Fainting	9	9.8
Nausea	3	3.29
Abdominal pain	2	2.19
Angioedema	2	2.19
Bradycardia	1	1.09
Venom Immunotherapy Initiation Time After Bee Sting		
1 month or less	4	9.3
1-2 months	18	41.9
2-6 months	5	11.6
6 months-1 year	12	27.9
1 year and above	4	9.3
Venom Immunotherapy Initiation Age		
5 years and under	3	7.0
5-10 years	18	41.9
10-15 years	7	16.3
15 years and above	15	34.9

Family Allergy History

When examining the family history of atopic diseases among the patients, it was determined that 51.1% had a family history of such diseases; of these, 8 (18.6%) had a family history of bee venom allergy. Among these patients, 2 had siblings, 3 had mothers, and the remaining 3 had fathers, uncles, or aunts with a history of bee venom allergy. One patient's father died due to complications resulting from bee stings related to this allergy. Moreover, 20.9% of the participants were directly involved in beekeeping or had family members engaged in this industry.

Skin Prick Test (SPT) and SpIgE Results

The results of the SPT were available for 41 patients, of whom 37 (90.2%) showed positive reactions. Among these patients, 15 (36.5%) were sensitive to *Apis mellifera*, 5

(12.1%) to *Vespula vulgaris*, and 17 (41.4%) showed sensitivity to both *Vespula vulgaris* and *Apis mellifera*. Additionally, the serum-specific IgE results of 27 patients were examined, revealing that 12 (44.4%) were positive for *Apis mellifera*, 7 (25.9%) for *Vespula vulgaris*, and another 7 (25.9%) showed positive reactions to both types of venom. Of the 28 patients with reported *Apis mellifera* allergy, 27 were diagnosed through test results, while 1 was diagnosed based on clinical symptoms and allergy history.

Bee Stings and Reactions

When evaluating allergies based on bee species, 28 patients (65.1%) were allergic to *Apis mellifera*, 9 (20.9%) to *Vespula vulgaris*, and 6 (14%) were allergic to both (Table 1).

Beekeeping in our region starts in April and continues until October. Of these cases, 26 (60.5%) encountered bees during the summer months (Table 1). It is observed that the most common season for bee stings is the summer season.

The locations of bee stings are as follows: arm (67.4%), hand (11.6%), under the eye (9.3%), foot (9.3%), and chest (2.3%). In our study, the evaluation of systemic reactions according to the Müller classification shows a wide spectrum of reaction severity, with Grade 1, 2, 3, and 4 reactions detected at rates of 4.7%, 9.3%, 37.7%, and 48.8%, respectively. Additionally, symptoms following bee stings include local swelling, shortness of breath, hypotension, redness, and respiratory distress. Allergic reactions observed in 43 patients after bee stings are summarized in Table 1.

When examining the time elapsed before symptoms appeared after bee stings, it was found that symptoms appeared within the first five minutes in 28 patients, between five and ten minutes in 12 patients, between ten and thirty minutes in 2 patients, and after thirty minutes in 1 patient. There was no significant difference found in the relationship between age, gender, location of bee sting, bee species, reaction severity, and the onset time of symptoms.

VIT and Side Effects

The patients included in the study received initial intervention treatment at the nearest healthcare center following bee stings and were subsequently referred to our outpatient clinic. Adrenaline was administered to 23 patients, while corticosteroids, antihistamines, and oxygen therapies were applied to 20 patients. Patients were evaluated at the Pediatric Allergy and Immunology Clinic and started VIT approximately 1 year after the bee sting that caused systemic reaction, with a range from 1 month to 9 years (Table 1). Among the patients who started VIT, the youngest was 4.5 years old, the oldest was 51 years old, and the median age was 11. Of the total 43 patients, 28 received *Apis mellifera* venom, 9 received *Vespula vulgaris* venom, and 6 received both *Apis mellifera* and *Vespula vulgaris* VIT.

Patients receiving VIT were closely monitored for side effects. During this period, allergic reactions occurred in 12 patients (10 males, 2 females). These reactions occurred after the first dose in 5 patients, and in the remaining patients, they occurred after subsequent doses. Local reactions were observed in 7 patients, while systemic reactions were observed in 5 patients. Among these patients, 11 had a personal or family history of atopic disease. Of the 5 patients experiencing systemic reactions, 4 were male, 1 was female, and the average age was 26.

Among the 43 patients receiving VIT, 22 were stung by bees during or after the treatment process. Of these patients, 21 were stung by the species they were undergoing treatment for. Among those stung, 14 showed no symptoms, while 6 experienced local and 2 experienced systemic reactions. Additional treatment was not administered to 18 patients stung by bees. Two patients were only given antihistamines, while steroid, antihistamine, and adrenaline treatments were applied to the other two patients. The treatment of 2 patients who showed anaphylaxis due to VIT was discontinued because they did not want to continue treatment. The treatment of 21 patients was completed in the fifth or sixth year. One patient discontinued treatment in the fourth year at their own discretion. The remaining 19 patients are still undergoing VIT.

Discussion

VIT is recognized as the sole and most effective disease-modifying treatment method for Hymenoptera venom allergy, affecting 3% of adults and 0.8% of children.[6] However, there are very few studies, especially involving children, that examine the reliability and efficacy of VIT. In this context, this study, including 43 patients aged between 5 and 56 years who applied to our faculty from the Central Black Sea region, makes a significant contribution to the literature. The results of our study showed that male gender is more at risk for bee venom allergy. This situation may have arisen due to the fact that males are more active in outdoor environments or more prone to activities such as beekeeping.

When examining the prevalence of atopic disease in children with venom allergy, it was stated that 33% of these patients had atopic disease, and 66% had previous experience with bee stings.[7] Consistent with the study conducted by Novembre et al.,[8] our study did not find a statistically significant relationship in terms of the incidence of atopic disease in patients with bee venom allergy. However, in our study, all patients who developed side effects during VIT had a personal or family history of atopic disease. This find-

ing indicates that special attention is required for patients with a history of atopic disease during VIT applications and that these patients may be more sensitive to side effects.

In the Central Black Sea region where beekeeping is prevalent, the probability of encountering honey bees and thus the risk of bee venom allergy increases. 68% of patients in our region were stung by honey bees, indicating the impact of regional factors on the prevalence of bee venom allergy. Similar to our study, in a study conducted by Clark et al.[9] in the United States, the most common site of stings was found to be the hands and arms. This may be attributed to the tendency for exposed areas of the body, such as the hands and arms, to be more prone to bee stings. However, no significant relationship was observed between the severity of reactions and the age at the time of stinging, the species of bee, gender, and the site of stinging.

The evaluation of systemic reactions according to the Müller classification in our study demonstrates that the severity of reactions encompasses a wide spectrum. Grade 1, 2, 3, and 4 reactions were detected at rates of 4.7%, 9.3%, 37.7%, and 48.8%, respectively, indicating that especially high-grade reactions constitute a significant portion. At the time of diagnosis, severe reactions (Müller grade 4) were observed in 21 patients, moderate reactions (Müller grade 2-3) in 20 patients, and mild reactions (Müller grade 1) in 2 patients. Compared with a multicenter study conducted in Europe, the distribution of reaction severity in our study is somewhat different. In the European study, systemic reactions developed after bee stings were evaluated in 840 patients, and grade 1, 2, 3, and 4 reactions were found at rates of 12%, 23%, 41%, and 24%, respectively.[10] This difference may stem from various factors such as regional variations, different species of bees, or demographic differences.

In a study conducted by Golden et al.,[11] it was reported that the rate of systemic reactions to bee stings in children who did not receive VIT was 17%, whereas in treated patients, this rate was 3%. In our study, out of 43 patients, 22 (51.2%) were stung by bees either while undergoing VIT or after completing VIT, yet only 2 patients experienced systemic reactions. This indicates that VIT is an effective method in reducing systemic reactions to bee stings and may provide increased protection against bee stings.

When evaluating the onset times of systemic reactions after bee stings in our study, it was found that reactions began within the first 10 minutes in 93% of cases, while in 2.3% of cases, reactions began after 30 minutes. Lockey et al.[12] reported that 51% of systemic reactions after bee stings began within the first 10 minutes, and in some cases, reactions began 5 hours later. Studies have shown that the shorter the onset time of the reaction in individuals allergic to *Apis mellifera*, the higher the severity of the reaction. However, contrary to the literature, our study did not find a significant difference in this regard.

In our study, 65.1% of the patients (28 patients) received VIT for *Apis mellifera*, 20.9% (9 patients) for *Vespula vulgaris*, and 14% (8 patients) for both *Vespula vulgaris* and *Apis mellifera*. The high rates of VIT treatment associated with bee venom allergy may indicate that patients involved in beekeeping may require this treatment more frequently.

Immunotherapy used in the treatment of bee venom allergy aims to prevent systemic reactions, although rare cases of systemic reactions related to immunotherapy may occur. However, considering the severity of bee sting allergy, it is important for VIT to be both highly effective and reasonably safe. According to traditional treatment protocols, systemic reactions related to treatment may occur in approximately 3% to 12% of patients.[13,14] These reactions are generally mild and easily treatable. In our study, 12 out of 43 patients (27.9%) experienced side effects during VIT. During application, local side effects were observed in 16.3% of patients, and systemic side effects in 11.6% of patients.

In our study, systemic reactions were observed in a total of 5 patients during immunotherapy treatment. Among these, 4 had *Apis mellifera* allergy, and 1 had both *Apis mellifera* and *Vespula vulgaris* allergies. According to the study by Lockey et al., the reported rates of adverse effects during immunotherapy were 40% for *Apis mellifera* and 12% for *Vespula vulgaris*, while Müller et al. reported adverse effects of 21% for bee venom and 4% for wasp VIT.[12,13] These results suggest that patients receiving VIT for bee venom allergy may have a higher risk of allergic reactions compared to wasp venom. Therefore, patients undergoing VIT for bee venom allergy may require more detailed evaluation before treatment.

Two of our patients experienced vaccine-related anaphylaxis and decided not to continue treatment, leading to the discontinuation of immunotherapy. Systemic reactions occurred immediately after vaccination, before reaching the maintenance dose. The common characteristic of these two patients was a history of drug allergy. However, in the literature, there is no significant association between VIT-related adverse effects and variables such as gender, age, concomitant cardiovascular diseases, asthma, or other allergic diseases, beta blockers, or ACE inhibitors.[14] The majority of VIT-related systemic reactions occur during the dose escalation phase at the beginning of treatment. Therefore, initial doses should be administered under the supervision of an allergy specialist before transitioning to maintenance doses. A multicenter study conducted by Nasser et al.,[14] as

well as a study by Lockey et al.[12] in the United States, similarly found that VIT-related systemic reactions were more common during the dose escalation period.

Among the 41 patients continuing VIT in our study, 22 (51.2%) were stung by bees while undergoing VIT. Of these, 21 were stung by the species of bee they were being treated for. While 14 of these incidents resulted in no reaction, 6 resulted in local reactions, and 2 resulted in systemic reactions. Eighteen patients did not require treatment, but 3 patients received antihistamine and/or steroid therapy. None of our patients required adrenaline. Two patients experiencing systemic reactions encountered bees at the beginning of treatment, highlighting the importance of patients carrying adrenaline auto-injectors when starting treatment.

Conclusion

This study provides important findings supporting the effectiveness and safety of VIT in the treatment of bee venom allergy. We demonstrate that VIT is effective in treating systemic reactions and may improve patients' quality of life. However, careful management of initial VIT doses and close monitoring of patients are necessary. Additionally, this study emphasizes the need for further research and clinical trials.

Disclosures

Ethics Committee Approval: This study was approved by the Ondokuz Mayis University Ethics Committee (date: 04.03.2022, number: 2022000001-1).

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Conflict of Interest: The authors declared no potential conflicts of interest.

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Informed consent: Consent for publication were obtained from the individuals involved or, in the case of children, from their parents or legal guardians.

Authorship Contributions: Concept – S.I.K.K., S.O.C., R.S.; Design – S.I.K.K., S.O.C., R.S.; Supervision – R.S.; Materials – S.I.K.K., S.O.C.; Data collection &/or processing – S.O.C.; Analysis and/or interpretation – S.I.K.K., S.O.C., R.S.; Literature search – S.I.K.K., S.O.C.; Writing – S.I.K.K., S.O.C.; Critical review – R.S.

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