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Original Article

Venom immunotherapy: A real-life experience in a tertiary referral center in Turkey

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Abstract

Aim: Venom allergy is an important health problem because of life-threatening reactions and impaired quality of life. The only treatment that can prevent the risk of a subsequent systemic sting reaction is venom immunotherapy. Additionally, there has been limited report about Hymenoptera venom immunotherapy practice from Turkey. In our clinic, which is an important allergy center in Turkey, we aim to share the clinical characteristics of venom immunotherapy patients and to raise awareness by sharing our experience about venom immunotherapy.

Materials and Methods: Between December 2012 and February 2019, adult patients who underwent venom immunotherapy in Uludag University Faculty of Medicine, Department of Immunology and Allergic Diseases outpatient clinic were evaluated. The sociodemographic characteristics of the patients, re-stings and reaction type during venom immunotherapy were recorded.

Results: A total of 52 patients (44.2% female, 55.8% men; mean age= 48.4 ± 12.9 years) were included. From a total of 52 patients, 41 (78.8%) received VIT with honey bee, 8 (15.4%) with wasp and 3 (5.8%) with honey bee and wasp. Only 4 (7.7%) patients developed systemic reactions due to venom immunotherapy. During the venom immunotherapy period, 19 (36.5%) patients were re-stung by the culprit bee and none of them had any systemic allergic reactions.

Conclusions: Our data is consistent with previous literature regarding safety and effectivenes of venom immunotherapy. We believe that any effort increasing knowledge of venom allergy is important.

Keywords: Hymenoptera; immunotherapy; venom allergy

INTRODUCTION

It is known that 56.6-94.5% of the general population have been stung at least once in their lifetime by Hymenoptera (1). The prevelance of hypersensitivity reactions to Hymenoptera venom is 5%-7.5% (2). The winged Hymenoptera that sting humans include Apis mellifera known as honey bees from the Apidae family, and Vespula vulgaris known as paper wasps or yellow jackets from the Vespidae family. While most sting reactions are manifested as painful, erythematous swelling localized (limited) to sting site and resolve spontaneously, some reactions can be fatal. Ig-E mediated reactions triggered by hymenoptera stings can be associated with large local reaction (LLR) (> 10 cm diameter, lasts longer than 24 hours) which is thought to be clinical presentation of a late-phase IgE mediated reaction or systemic reactions (SRs) (3). Systemic reactions are manifested in a wide clinical spectrum ranging from mild cutaneous reactions to life-threatening multiple organ involvement. In Europe, the prevalence of LLR due to hymenoptera stings is estimated to range between 2.4% and 26.4%, whereas that of SR vary between 0.3%-7.5% (4,5). In some special groups, for example beekeepers, this rate may be higher. In our previous study with 221 beekeepers in Bursa province, it was observed that 7.3% had LRR and 37.6% had SR due to bee stings (6).

The only treatment that can prevent the risk of a subsequent systemic sting reaction is venom immunotherapy (VIT) and it has been reported to be effective in 77-84% and 91-96% of patients treated with honeybee venom and vespid venom, respectively (7,8). Quality of life may be significantly impaired in patients with a history of systemic reaction due to re-sting and fear of death. VIT also improves quality of life in these patients (9). Despite effectiveness of VIT, there are limited published data about Hymenoptera VIT practice from our country. As far as we

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know, this is the first reported study to investigate venom immunotherapy practice from southeast of the Marmara Sea, Northwest of Turkey.

Venom allergy is an important health problem because of life-threatening reactions and impaired quality of life. Severe reactions are unpredictable and may progress within 15 minutes that no treatment can be given before respiratory or cardiac arrest. Furthermore, these reactions can cause a rapid death even if optimal treatment is given immediately (10). Because of the low awareness of VIT in the management of Hymenoptera venom allergy, we aimed to share our experiences and the data of VIT patients in our clinic.

MATERIALS and METHODS

Study Design

All adult patients treated with VIT from December 2012 to February 2019 in Department of Immunology and Allergic Diseases outpatient clinic were included and retrospectively evaluated. There was no patient excluded from the study. Patients who had a sting-induced systemic allergic reaction it was confirmed diagnosis of hymenoptera venom allergy by either skin tests and/or serum spesific IgE detection during hospital admission. The study was approved by the institutional ethics committee of Uludag University (identification 2019 2/20). Since it was a retrospective study, consent was not obtained from the patients.

The sociodemographic characteristics of the patients (age, sex, place of residence, history of village life and beekeeping), presence of comorbid diseases (asthma, allergic rhinitis, cardiovascular disease, autoimmune diseases), laboratory parameters (serum total IgE, eosinophil and tryptase values), serum specific IgE and skin prick test results (honey bee and wasp) before VIT and at least 1 year later of VIT, severity of systemic allergic reactions to Hymenoptera stings, type of VIT (honey bee / wasp), duration of VIT, reactions (local / systemic) during VIT, re-stings and reaction type during VIT were recorded.

Systemic reactions are graded into four groups according to the classification by Ring and Messmer: Grade 1, generalized skin lesions (rash, urticaria, angioedema); Grade 2, mild to moderate pulmonary, cardiovascular and / or gastrointestinal symptoms; Grade 3, anaphylactic shock, loss of consciousness; Grade 4 was defined as cardiac and/or respiratory arrest (11).

Venom immunotherapy protocol

Venom immunotherapy involves the administration of gradually increasing doses of allergen extracts to induce immunological and clinical tolerance of responsible allergens. There are two important phases: build up phase and maintenance phase. Typically, patients receive a series of subcutaneous injections, starting with very low concentrations of allergen until the maintenance dose is achieved. Besides the conventional protocols, where the maintenance dose is generally achieved after a series of weekly injections, several alternative up-dosing regimens can be performed to reach the maintenance dose faster. In the maintenance phase, the injections are continued at 4 to 6-week intervals for 3 to 5 years. Patients are evaluated by physicians before each injection and kept under medical surveillance for at least half an hour after injection.

In our study, VIT was administered according to the recommendations of the National Guideline for Allergen İmmunotherapy (12).

Statistical analysis

Fisher's Exact test, Fisher Freeman Halton test, Shapiro-Wilk test were used for data distribution. Oneway Anova test was used for parametric variables and Wilcoxon Signed Ranks test was used for non-parametric variables. Statistical analysis was performed using SPSS (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0, Armonk, NY: IBM Corp.), and $p < 0.05$ was considered statistically significant.

RESULTS

A total of 52 patients (44.2% female, 55.8% men; mean age= 48.4 ± 12.9 years) receiving VIT enrolled in this study. Demographic and clinical data are summarized in Table 1. Out of all the patients, 24 (46.2%) and 28 (53.8%) were living in urban and rural areas, respectively. Twenty-two (42.3%) of the patients were beekeepers; most of these beekeepers (81.8%) were male. The disease most commonly accompanying Hymenoptera allergy in our patients was allergic rhinitis (40.4%); followed by cardiovascular diseases (26.9%), asthma (13.5%), thyroid diseases (9.6%) and diabetes mellitus (5.8%). The median basal serum tryptase level was 4.11 µg/L (min: 1-max: 26.9). Three patients had high tryptase levels (> 11.4 µg/L), whereas none of these patients had mast cell disorder. The median serum total IgE was 88.4 IU/ml (min: 3.3-max: 1799) and the peripheral blood eosinophil count was 185 cells/µL (min: 20-max: 1030).

The severity of index allergic reactions after Hymenoptera stings according to Ring-Messmer classification is shown in Figure 1. A high frequency of grade 3 reactions (53.8%) was reported. No statistically significant relationship was found between systemic reaction severity and gender or age ($p= 0.49$ and $p= 0.11$, respectively for both comparisons). There was also no statistically significant difference between index reaction severity among patients with and without asthma ($p= 0.37$). Two (28.6%) of the patients with asthma had grade 1, 3 (42.9%) had grade 2 and 2 (28.6%) had grade 3 systemic reactions. From a total of 52 patients, 41 (78.8%) received VIT with honey bee, 8 (15.4%) with wasp and 3 (5.8%) with honey bee and wasp. Only 4 (7.7%) patients developed systemic reactions due to VIT. During the VIT period, 19 (36.5%) patients were re-stung by the culprit bee. While 68.4% of these patients did not develop reactions, local reactions were observed in 31.6% (Table 2).

Looking at the the patients skin prick test sensitivity with

honey bee venom, a significant decrease was observed after VIT (mean diamater= 3.8 ± 1.72 mm vs 2.1 ± 1.75 mm, p< 0.05). However, decrease in skin prick test sensitivity with wasp venom was not significant (mean diamater= 3.6 ± 1.41 mm vs 2.8 ± 1.3 mm, p= 0.48).

The median duration of VIT was 30 months (min: 1-max: 157 months). The adherence rate to VIT in our study was high; only one patient discontinued her treatment. In 7 patients, VIT was terminated after 5 years. Two out of the 52 patients received prolonged treatment (more than 5 years) because of the high risk of developing systemic allergic reactions.

Table 1. Demographic and clinical characteristics of patients

	Honeybee VIT	Wasp VIT	Honeybee and Wasp VIT	Total
Patients n (%)	41 (78.8)	8 (15.4)	3(5.8)	52 (100)
Age (year) (±std)	49.4 (12.33)	47.7 (15.23)	36.7 (11.85)	48.4 (±12.9)
Gender				
Female-n (%)	18 (43.9)	4 (50)	1 (33.3)	23 (44.2)
Male-n (%)	23 (56.1)	4 (50)	2 (66.7)	29 (55.8)
Allergic rhinitis-n (%)	14 (34.1)	5 (62.5)	2 (66.7)	21 (40.4)
Cardiovascular disease-n (%)	12 (29.3)	2 (25)	0	14 (26.9)
Asthma-n (%)	5 (12.2)	1 (12.5)	1 (33.3)	7 (13.5)
Thyroid disease-n (%)	4 (9.7)	1 (12.5)	0	5 (9.6)
Diabetes Mellitus-n (%)	2 (4.9)	1 (12.5)	0	3 (5.8)
Beekeeping -n (%)	20 (48.8)	1 (12.5)	1 (33.3)	22 (42.3)
Severity of systemic reaction with index bee sting -n (%)				
Grade 1	4 (9.7)	2 (25)	2 (66.7)	8 (15.4)
Grade 2	12 (29.3)	2 (25)	1 (33.3)	15 (28.8)
Grade 3	24 (58.5)	4 (50)	0	28 (53.8)
Grade 4	1 (2.4)	0	0	1 (1.9)

VIT: venom immunotherapy

Table 2. Characteristics of patients re-stung by the culprit bee during venom immunotherapy

Patient No	Gender/ Age	SAR severity after bee sting	Type of VIT	Reaction to Hymenoptera sting after VIT
1	F/57	Grade 3	Honeybee	none
2	M/50	Grade 3	Honeybee	none
3	M/43	Grade 2	Honeybee	none
4	F/31	Grade 3	Honeybee	none
5	M/50	Grade 2	Honeybee	none
6	M/65	Grade 3	Honeybee	none
7	F/61	Grade 3	Wasp	none
8	M/23	Grade 2	Honeybee +Wasp	none
9	M/64	Grade 3	Honeybee	local
10	M/54	Grade 1	Honeybee	local
11	M/25	Grade 3	Honeybee	none
12	M/54	Grade 3	Honeybee	local
13	M/42	Grade 3	Honeybee	local
14	M/53	Grade 2	Honeybee	local
15	M/68	Grade 3	Honeybee	none
16	M/36	Grade 3	Honeybee	none
17	F/57	Grade 2	Honeybee	local
18	M/44	Grade 1	Honeybee + Wasp	none
19	M/49	Grade 2	Honeybee	None

VIT: venom immunotherapy

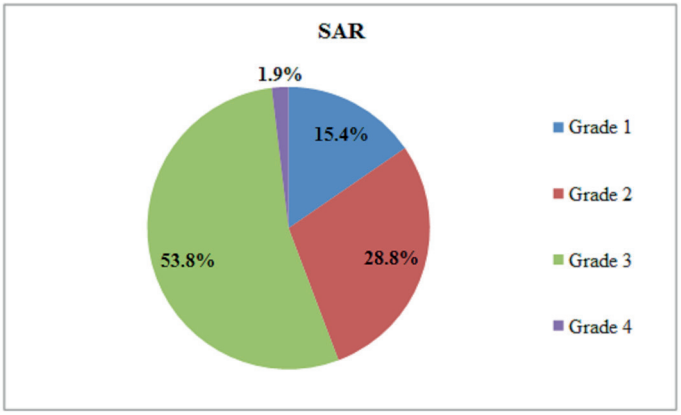

Figure 1. Distribution of systemic allergic reactions (SAR) caused by index Hymenoptera stings according to Ring-Messmer classification

DISCUSSION

In our study, the mean age was 48.4 (± 12.9), and no significant relationship was found between age and reaction severity. Venom allergy can develop at any age, but more severe reactions occur in adults and most deaths occur in this age group (13). Twenty-nine (55.8%) of our patients were males and 62.1% of them were beekeepers. Similar to our study, it is thought that men are affected more frequently than women, and this is related to the prevalence of outdoor occupations (14-16). Beekeepers pose the highest risk (16).

In our study, 15.4% of the patient's experienced grade 1 Hymenoptera sting reactions before VIT, 28.8% grade 2, 53.8% grade 3 and 1.9% grade 4. In a study of Albuhairi et al. that evaluated 78 patients with 22-year bee allergies, before venom immunotherapy 11.6% of patients had severe, 72.7% had moderate, and 10.4% had mild systemic reactions histories (17).

The prevelance of LLRs ranges from 2.4% to 26.4% in the general population [4]. In our study, there was no patient receiving VIT due to LLRs. VIT is not routinely recommended for these patients given the relatively low risk of serious reactions with subsequent stings (0.8 - 7%) (18,19). However, VIT may be considered a treatment option for adult patients with recurrent, troublesome LLRs to reduce the duration and size of future LLRs (20).

The treatment of Hymenoptera stings consists of the treatment of acute reaction, taking protective measures to minimize re-encounter, informing the patient about the use and necessity of adrenalin autoinjector in case of anaphylaxis and starting VIT in selected patients. Venom immunotherapy, which is the most effective method of treatment, reduces the risk of having a serious allergic reaction by 90% (21). Patients with bee allergies were found to have a 30 to 60% risk of anaphylaxis if not treated with VIT (22). In our study, 19 (36.5%) patients were re-stung by the culprit bee during the VIT and none of them had any systemic allergic reactions. Clinical efficacy is unknown in 33 patients who were not stung by the culprit bee during VIT. In this case, sting challenge test can be performed to evaluate clinical efficacy, but for ethical reasons, this method is not applied to our patients.

While most patients tolerate VIT well, some may experience local and systemic reactions during treatment. Four (7.7%) of our patients developed systemic allergic reactions due to VIT. In a multicenter prospective study in Europe, 20% of 840 VIT patients aged 5-77 years experienced systemic reactions due to VIT (23). Systemic reactions have been reported in 12% of 1410 VIT patients treated in the USA between 1979 and 1982 (24). The lower risk of systemic reactions in our patients may be related to differrences in up-dosing regimens and type of extracts to be used.

There is no simple, low-cost test or biomarker with high sensitivity and specificity to monitor effectiveness of VIT. Serum venom specific IgE testing can be used for diagnosis, but routine use to monitor VIT success is not recommended. It has been reported that venom skin tests have become negative after 5 years of VIT in 20% of adults (25). In our patients, skin prick test sensitivity to honey bee and wasp venoms decreased after VIT. If skin test reactivity increase or does not decrease, re-evaluation of the patient is recommended (12).

Although VIT is currently considered the only disease-modifying treatment option, many patients with hymenoptrea venom allergy are not referred to allergy specialists for further evaluation, and patients are deprived of this potentially life-saving treatment option (5). Çatal et al. found that only 38% of family physicians have knowledge of VIT (26). On the other hand, a previous study from our group revealed that although 49.8% of beekeepers were aware of VIT treatment, 63.2% of them thought bee allergy was incurable (6). It shows that patients do not have enough information about the effectiveness of VIT, and how important it is for the patients to be directed properly by the health professionals. It's particularly important for health professionals working in primary health care and emergency services to refer patients with a history of systemic sting reaction to a specialist center for further examination and treatment.

This study has some limitations: retrospective nature of the study, small number of study population and lack of clinical data concerning the patients who did not re-sting by the culprit bee.

CONCLUSION

Despite the small number of patients, our data is consistent with previous literature regarding safety and effectivenes of VIT. Finally, hymenoptera venom allergy represents an important and neglected public health problem with risk of systemic reactions which can also be fatal. We believe that any effort increasing knowledge of venom allergy will provide the opportunity of appropriate management of the disease. It may be beneficial to give education (eg indication, effectiveness, side effect) to health care providers in our hospital about VIT and to share our experiences about our patients. In addition, giving VIT training to especially beekeepers can help raise awareness

about treatment. We need to increase awareness about venom allergy among patients and produce more studies to investigate VIT practice.

Competing interests: The authors declare that they have no competing interest.

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Ethical approval: The study was approved by the institutional ethics committee of Uludag University (identification 2019 2/20).

REFERENCES

1. Antonicelli L, Bilo MB, Bonifazi F. Epidemiology of Hymenoptera allergy. Curr Opin Allergy Clin Immunol 2002;2:341-6.
2. Antolín-Amérigo D, Moreno Aguilar C, Vega A, et al. Venom immunotherapy: an updated review. Curr Allergy Asthma Rep 2014;14:449.
3. Ludman SW, Boyle RJ. Stinging insect allergy: current perspectives on venom immunotherapy. J Asthma Allergy 2015;8:75-86.
4. Bilo MB, Bonifazi F. The natural history and epidemiology of insect venom allergy: clinical implications. Clin Exp Allergy 2009;39:1467-76.
5. Bilò BM, Bonifazi F. Epidemiology of insect-venom anaphylaxis. Curr Opin Allergy Clin Immunol 2008;8:330-7.
6. Ediger D, Terzioglu K, Ozturk RT. Venom allergy, risk factors for systemic reactions and the knowledge levels among Turkish beekeepers. Asia Pac Allergy 2018;8:e15.
7. Muller U, Helbling A, Berchtold E. Immunotherapy with honeybee venom and yellow jacket venom is different regarding efficacy and safety. J Allergy Clin Immunol 1992;89:529-35.
8. Rueff F, Vos B, Elberink JO, et al. Predictors of clinical effectiveness of Hymenoptera venom immunotherapy. Clin Exp Allergy 2014;44:736-46.
9. Oude Elberink JN, De Monchy JG, Van Der Heide S, et al. Venom immunotherapy improves health-related quality of life in patients allergic to yellow jacket venom. J Allergy Clin Immunol 2002;110:174-82.
10. Pumphrey RS. Lessons for management of anaphylaxis from a study of fatal reactions. Clin Exp Allergy 2000;30:1144-50.
11. Ring J, Laubenthal H, Messmer K. Incidence and classification of adverse reactions to plasma substitutes. Klin Wochenschr 1982;60:997–1002.
12. Sin BA, Şahiner Ü. Allergen İmmunotherapy: National Guideline. Asthma Allergy Immunol 2016;14:1-119.
13. Ebo DG, Hagendorens MM, Stevens WJ. Hymenoptera venom allergy. Expert Rev Clin Immunol 2005;1:169-75.
14. Tang ML, Osborne N, Allen K. Epidemiology of anaphylaxis. Curr Opin Allergy Clin Immunol 2009;9:351-6.
15. Graft DF. Insect sting allergy. Med Clin North Am 2006;90:211-32.
16. Toletone A, Voltolini S, Passalacqua G, et al. Hymenoptera venom allergy in outdoor workers: Occupational exposure, clinical features and effects of allergen immunotherapy. Hum Vaccin Immunother 2017;13:477-83.
17. Albuhairi S, El Khoury K, Yee C, et al. A twenty-two-year experience with Hymenoptera venom immunotherapy in a US pediatric tertiary care center 1996-2018. Ann Allergy Asthma Immunol 2018;121:722-8.
18. Golden DB, Kagey-Sobotka A, Norman PS, et al. Outcomes of allergy to insect stings in children, with and without venom immunotherapy. N Engl J Med 2004;351:668-74.
19. Mauriello PM, Barde SH, Georgitis JW, et al. Natural history of large local reactions from stinging insects. J Allergy Clin Immunol 1984;74:494-8.
20. Sturm GJ, Varga EM, Roberts G, et al. EAACI guidelines on allergen immunotherapy: Hymenoptera venom allergy. Allergy 2018;73:744-64.
21. Boyle RJ, Elremeli M, Hockenhull J, et al. Venom immunotherapy for preventing allergic reactions to insect stings. Cochrane Database Syst Rev 2012;10:CD008838.
22. Reisman RE. Natural history of insect sting allergy: relationship of severity of symptoms of initial sting anaphylaxis to re-sting reactions. J Allergy Clin Immunol 1992;90:335-9.
23. Mosbech H, Muller U. Side-effects of insect venom immunotherapy: results from an EAACI multicenter study. European Academy of Allergology and Clinical Immunology. Allergy 2000; 55:1005-10.
24. Lockey RF, Turkeltaub PC, Olive ES, et al. The Hymenoptera venom study. III: Safety of venom immunotherapy. J Allergy Clin Immunol 1990; 86:775-80.
25. Golden DB, Kwiterovich KA, Kagey-Sobotka A, et al. Discontinuing venom immunotherapy: outcome after five years. J Allergy Clin Immunol 1996;97:579-87.
26. Catal F, Topal E, Celiksoy MH, et al. The knowledge of primary care physician's about bee venom allergy treatment and adrenaline auto injector usage skills. J Turgut Ozal Med Cent 2014;21:33-6.