
Long-term efficacy of venom immunotherapy

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Background: The long-term efficacy of venom immunotherapy (VIT) in patients who either prematurely discontinued VIT or who experience subsequent stings after discontinuation of VIT remains uncertain.

Objective: To survey sting reaction patterns in patients who had previously discontinued VIT.

Methods: Patients who had received VIT between January 1, 1984, and December 31, 2004 were sent a questionnaire inquiring whether they had been stung by an insect to which the VIT had been directed. Symptoms that developed were assessed. The patients were subsequently contacted by telephone to clarify their responses.

Results: Of 227 patients who responded to the questionnaire, 181 (79.7%) received VIT for more than 3 years; 100 of these 181 patients (55.2%) were stung after discontinuing VIT. At the time of the first sting after stopping VIT, 92 patients had a local reaction and 8 had a systemic reaction. Of 40 patients who were stung more than once after ending VIT, 7 (17.5%) experienced reactions of greater severity with the subsequent stings. All the patients reported that their reactions after ending VIT were milder than before treatment. The likelihood of systemic reactions to stings was almost identical in patients treated for either longer or shorter than 3 years with VIT.

Conclusions: In most patients, VIT provides long-term protection from severe systemic reactions. Risk of systemic reactions increases with subsequent stings after ending VIT. All the patients reported that symptoms experienced with stings after stopping VIT were milder than symptoms before VIT.

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INTRODUCTION

The main goal of immunotherapy in venom-allergic patients is to reduce the possibility of a life-threatening anaphylactic reaction to a sting. Therefore, venom immunotherapy (VIT) is indicated in patients with severe systemic reactions, including those classified as Mueller grade 3 or 4.¹ After a buildup phase of VIT, a maintenance dose of 100 μ g of venom is repeated every 4 weeks during the first year of treatment and every 6 to 8 weeks during subsequent years. Some studies^{2,3} suggest that the maintenance dose can safely be administered every 3 months for most patients. The decision to stop VIT is difficult and depends on several factors, including the duration of VIT, the likelihood of the occurrence of a sting, the occurrence of adverse effects during VIT, and results of clinical tests of venom sensitivity. The VIT may be stopped after 3 to 5 years, especially if there were no systemic adverse effects during VIT, or when skin prick test results and venom specific IgE levels have become negative.⁴ The most reliable indicator of successful treatment is a well-tolerated controlled or accidental insect sting.^{5–7} In Slovenia, VIT was first implemented in 1984. This study evaluates the long-term effectiveness of VIT in patients after the cessation of treatment and investigates whether VIT prevents severe systemic reactions several years after the end of treatment and even after repeated insect stings.

METHODS

Patients treated with VIT because of severe allergic reactions to bee, wasp, or hornet stings and who subsequently discontinued VIT between January 1, 1984, and December 31, 2004, were included. Their addresses were located using the hospital information system.

Study Design

The study was approved by the state ethics committee. Patients who underwent immunotherapy for any allergic disorder, including allergic rhinitis, allergic asthma, and venom allergy, between January 1, 1984, and December 31, 2004 were mailed a questionnaire. The questions asked included whether they had any accidental stings after concluding VIT and what reaction, if any, occurred after the sting. Patients were asked for their telephone numbers so that details about their sting reactions could be determined via a telephone interview. Patients who were stung after the end of VIT were then contacted by telephone to confirm the data in the questionnaire and were also asked additional questions related to the sting. The first inquiry was sent in July 2004, and the follow-up interviews were conducted in July and August 2004. Nonresponders to the questionnaire were sent another mailing in November 2004, followed by further telephone interviews. Data from incomplete or incorrectly completed questionnaires that were unconfirmed by telephone interviews were excluded from the study.

The telephone interviews collected the following information: (1) whether patients were certain that the sting that occurred after conclusion of VIT was made by the same type of stinging insect to which they were previously allergic and for which they had received VIT, (2) the time that had elapsed from the conclusion of VIT to the first subsequent

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sting, (3) the clinical symptoms and physical findings that resulted from the first sting after conclusion of VIT, (4) the number of times that patients were stung by the same insect after concluding VIT, (5) a precise description of the reaction to each sting that occurred after concluding VIT, (6) whether the reactions to the stings became more severe with subsequent insect stings, and (7) the opinion of the patient about the effectiveness of their VIT.

Data Analysis and Statistical Analysis

Data from the mailed questionnaires and the telephone interviews were recorded in a spreadsheet program (Excel 2003; Microsoft Corp, Redmond, Washington). Patients were divided into 2 groups: (1) those who were stung after VIT and (2) those who were not stung after VIT. Patients were further subdivided into 2 groups: (1) those who received VIT for 3 years or longer and (2) those who prematurely ended VIT before 3 years of treatment. Patients who prematurely ended VIT were analyzed as a separate group. Based on the insect sting reaction, patients were categorized into 2 groups: (1) those with local reactions to the sting, including pain, swelling, redness, and itching, and (2) those with systemic reactions to the sting.

Results for each group are presented as the number and percentage of patients who were stung after receiving VIT. From the group of patients who were stung after VIT, a subgroup of patients who were stung more than once was identified. Insect sting reactions in patients in this group were analyzed, comparing the severity of reactions to each sting. An increase in the severity of the reactions after repeated stings was defined as systemic reactions after a previously well-tolerated sting or increasing severity of systemic reaction.

Elapsed time from the first sting to the onset of more severe sting reactions was calculated. The likelihood of systemic reactions to stings was compared by analyzing the reaction occurrence in the group that completed VIT vs the group that prematurely ended VIT (χ^2 test). Data are displayed as mean (SD).

RESULTS

Survey questionnaires were mailed to 645 selected patients; 368 patients replied, yielding a response rate of 57.1%. Of those who responded, 139 patients were not treated with VIT. Based on information obtained from relatives, 20 patients were noted to have died after the end of treatment for various reasons unrelated to their allergic reactions. It was not possible to obtain any further information about their venom allergy. Sixty-one patients had moved and could not be contacted. Two treated patients returned questionnaires with insufficient data for evaluation. Because we could not reach them by telephone, those 2 patients were excluded from analysis. The remaining 227 patients who had received VIT were analyzed: 108 were treated with bee venom, 100 with wasp venom, and 19 with both venoms. The mean (SD) treatment duration was 4.16 (1.53) years, with the VIT period

ranging from 1 month to 10 years. Treatment was completed with the VIT being administered for at least 3 years in 181 patients (79.7%). In this group, VIT lasted 4.7 (0.95) years. Forty-six patients, representing 20.3% of all patients receiving VIT, ended treatment prematurely. In this group, VIT lasted 1.5 (0.5) years. The cause of premature termination of VIT was not determined.

In the group treated for longer than 3 years, 100 (55.2%) had an accidental field sting by the same insect to which they were allergic after concluding VIT. The first sting occurred 2.8 (1.8) years after concluding VIT, with an interval from concluding VIT to the first sting ranging from 1 month to 15 years. After the first sting, 92 patients (92.0%) had a local reaction, with redness, swelling, pain, or itching, and 8 (8.0%) had a systemic allergic reaction (3 with only skin symptoms and 5 with respiratory symptoms) (Table 1).

Forty patients (40.0%), 26 of whom had been treated with wasp venom, received several stings after the end of VIT. Fifteen patients had 2 stings, 9 had 3 stings, and 16 had more than 3 stings. Most of these patients (82.5%) had no reaction even after repeated stings (Table 2). Seven patients (17.5%) experienced systemic reactions: 4 were stung by wasps and 3 by honeybees. Six patients developed a reaction after first having a well-tolerated sting, and 1 patient had a more severe systemic reaction after a later sting. In 2 patients, more severe reactions occurred after the second sting but milder reactions after the third sting. Worsening of the sting reactions occurred 3.75 (1.5) years (range, 1–7 years) after the first sting. Assessing all stings and all reactions in the group of patients who finished VIT, 14 (14.0%) had a systemic reaction after stopping VIT.

In the group of patients who prematurely ended VIT, 26 (56.5%) experienced a field sting. The first sting occurred 2.7 (1.4) years after stopping VIT. Local reactions, with pain, redness, swelling, or itching, occurred in 21 patients (80.8%). Five patients (19.2%) had a systemic allergic reaction to the sting: 3 had only skin symptoms and 2 experienced respiratory symptoms (Table 1). The reactions were not more likely in patients who received VIT for a very short time. There was no difference in the probability of a systemic reaction after VIT between those who received VIT for longer than or shorter than 3 years ($\chi^2 = 1.73$; $P > .05$). In this group who

Table 1. Reactions to the First Sting After VIT in the Group That Successfully Concluded VIT vs the Group That Prematurely Ended VIT^a

	Patients, No. (%)	
	Successfully completed VIT	Prematurely ended VIT
Local reaction	92 (92)	21 (81)
Systemic reaction	8 (8)	5 (19)

Abbreviation: VIT, venom immunotherapy.

^a There was no significant difference in the probability of a systemic reaction comparing the 2 groups ($\chi^2 = 1.73$; $P > .05$).

Table 2. Treatment Outcomes in Patients With More Than 1 Sting After Ending VIT

Treatment outcome	Patients, No.
No reaction to any sting	33
No reaction to the first sting but a reaction to subsequent stings	4
Reaction to the first sting and a more severe reaction to subsequent stings	1
Reaction to the second sting but no reaction to subsequent stings	2
Total	40

Abbreviation: VIT, venom immunotherapy.

received field stings, 13 (50%) had several stings. None of them experienced worsening of their sting reactions with subsequent stings. In both groups, all the patients, regardless of their current sting reaction pattern, reported in their questionnaires or telephone inquiries that the reactions they experienced after concluding VIT were milder than those before VIT.

DISCUSSION

Introduced 30 years ago, VIT has been widely used for the past 15 years.⁸ The main goal of VIT is to reduce the likelihood of a life-threatening anaphylactic reaction. In an American study,⁹ 40% of people who died of allergic reactions to insect stings succumbed to their first allergic reaction. These deaths could not have been prevented by use of immunotherapy.⁹ Allergic reactions can diminish with time, especially in milder cases.^{10,11} Consequently, VIT is recommended only for patients with severe allergic reactions to insect stings.^{5,11,12} The long-term efficacy of VIT has been difficult to evaluate clinically. Even in patients in whom skin prick test results had become negative, systemic allergic reactions have been described and fatal or near fatal cases have been reported after the conclusion of VIT.^{13,14} The best confirmation of the efficacy of VIT is a sting by the insect to which the patient was allergic. This method is also used in most studies of the short- and long-term efficacy of VIT. Some studies recorded accidental field stings, and others performed deliberate sting challenges in a hospital setting, with only a few studies published about the long-term effectiveness of VIT.^{14–18} Furthermore, local epidemiologic circumstances must be considered. American and north European studies primarily include patients allergic to wasp venom. Patients in the present study are equally likely to be allergic to bee and wasp venom. Epidemiologic data have demonstrated the importance of a high-risk group of patients allergic to bee venom.¹⁹ This makes these data, including wasp and bee venom-allergic patients, especially interesting.

In the present study, accidental field stings after the end of treatment were evaluated. To obtain objective data demonstrating the long-term efficacy of VIT, very broad selection criteria were used to include patients in this study. The only inclusion criterion was that patients initiated and subse-

quently ended VIT. Patients were not stratified by the severity of their reactions before VIT, by which venom they were allergic to, by the occurrence of complications during VIT, or by specific IgE levels and skin prick test results before or after VIT. However, they were divided into 2 groups related to the duration of VIT. This allowed evaluation of the impact of treatment duration on therapeutic efficacy. The initial contact with venom-sensitive patients was via a mailed questionnaire because this was believed to be least burdensome for patients and allowed outreach to a large number of patients in a relatively short period. The survey was short because its primary goals were to determine whether patients had experienced a sting after concluding VIT and to acquire their telephone numbers. Regardless of the questionnaire simplicity, some incorrectly completed surveys were sent back by patients. In most cases, these patients described symptoms they received after stings before rather than after VIT. To correct these errors and to obtain additional data, the patients were contacted by telephone.

Despite review of the data from the mailed questionnaire during the telephone interviews, it must be remembered that all data obtained were subjective evaluations of symptoms from patients, who potentially could underestimate or overestimated the severity of their symptoms. As an example, 1 patient reported difficulty breathing after a sting, but during a later examination, which included a detailed clinical history discussion, it was revealed that most likely a psychogenic reaction or panic attack had actually occurred. This information was integrated into the overall results.

Of 227 patients included in this study, more than half (55.5%) experienced a field sting after cessation of VIT. The probability of a field sting was similar in the studies by Golden et al,^{14,17} namely, 50% to 62%. In the group that finished at least 3 years of VIT, after several years, only 8.0% reacted with systemic allergic reactions to the first sting. Thus, 92.0% of patients were protected by VIT at the time of the first sting after stopping VIT. Before VIT, all the patients reacted with a severe systemic reaction to stings. Patients who still had allergic reactions after concluding VIT reported that these reactions were milder than before VIT.

Similar data have been reported in other studies. In a study by Lerch and Muller¹⁸ that included 200 patients, of whom 120 were allergic to bee venom and 80 to wasp venom, 12.5% had systemic reactions occurring up to 7 years after VIT. Golden et al¹⁷ noted that 10% of systemic reactions occurred 5 years after VIT, including 8 treated with bee venom and 66 with wasp venom. A study by van Halteren et al¹⁶ indicated that 8% of patients allergic to wasp venom had systemic reactions after VIT. In their study, the systemic reactions were milder after VIT, with only a few life-threatening reactions noted. The efficacy of treatment was greater in wasp venom-sensitive patients than in those who were bee venom sensitive. A possible explanation is that bees inject more venom per sting than wasps, with the amount of bee venom injected during a sting always being similar. Because wasps

inject different amounts of venom during every sting, reactions after wasp stings are more unpredictable.^{18–20}

In the subgroup that had several stings after the conclusion of VIT, the present study noted a 17.5% reaction rate, which was a slightly greater percentage of systemic reactions than in other studies. This finding could be interpreted as diminishing treatment efficacy across time and after several stings. These results also contradict the findings of Golden et al,¹⁷ who reported that there were no increases in systemic reactions or even in resensitization after several stings subsequent to the conclusion of VIT. These data should be interpreted with some caution, however, because the present study had only 40 patients in this group, of whom 7 experienced a reaction after a first well-tolerated sting or worsening of reactions after subsequent stings. Most of these patients had only 2 or 3 stings, and, as described previously, at times a more severe reaction occurred after the second sting but a milder reaction after a subsequent sting.

In the subgroup that prematurely terminated VIT, the 19.2% reaction rate to stings was slightly greater but was not statistically significantly different from the rate in patients who had received VIT for more than 3 years. A similar value of 13% was described previously by Golden et al.¹⁵ Similar to the present study, Golden et al also concluded that the number of patients was too small to make definitive conclusions. In the present study, these reactions occurred in only 5 of 26 patients compared with 3 of 24 in the study by Golden et al. Thus, the percentage of systemic reactions is significantly less after premature discontinuation of VIT compared with an untreated population, where 50% to 70% of patients can expect to have another systemic reaction if stung soon after the first systemic reaction. Also, the natural disappearance of venom allergy has been described, which further reduces the possibility of a subsequent systemic reaction to 20% after 10 to 20 years.^{11,15}

In conclusion, the data collected in the present study demonstrated that most patients with severe systemic reactions before VIT have protection from anaphylactic reactions after VIT. Only 8.0% of the patients experienced a systemic reaction to the first sting after VIT. However, up to 17.5% of repeatedly stung patients can expect worsening of their reactions with subsequent stings. All patients with an allergic reaction after completing VIT confirmed that the reaction they experienced was milder than the reactions before VIT.

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