

Clinical and immunologic follow-up of patients who stop venom immunotherapy

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We prospectively studied 51 self-selected Hymenoptera sting-sensitive patients to determine (1) whether a minimal or optimal duration for venom immunotherapy (VIT) exists and (2) whether clinical or immunologic parameters exist that are predictive of clinical immunity after VIT was stopped. After 2 to 10 years of VIT, all patients had deliberate sting challenges (DSCs) from live insects. If DSCs were tolerated, patients voluntarily stopped VIT and returned annually for repeat venom skin tests (VSTs) and DSCs. In most patients, it was possible to monitor VST and venom-specific antibody (Ab) levels before and after VIT was stopped. One-year after VIT, VST and venom-specific IgE and IgG Ab level results were variable; 49 patients tolerated DSC, whereas two patients exhibited generalized reactions. These two patients had pre-VIT histories of grade IV field-sting reactions and had received VIT for 2 years and 4 years, respectively. The short-term (1 year) risk of recurrence of clinical allergy to stings after VIT was higher in patients who had experienced grade IV field-sting reactions before VIT versus patients experiencing grade I to III reactions before VIT (2/15, 13% versus 0/36, 0%) and higher in patients who had received VIT for less than 5 years versus patients who received VIT for 5 or more years (2/20, 10% versus 0/31, 0%). We suggest that VIT should be continued for 5 years in patients with pre-VIT field-sting reactions of grade IV severity. VST and venom-specific Ab results do not reliably predict the outcome of DSC or the subsequent clinical course in individual patients stopping VIT. (J ALLERGY CLIN IMMUNOL 1991;88:339-48.)

Key words: Hymenoptera, venom, immunotherapy, IgE antibodies, IgG antibodies

Hymenoptera VIT is effective in preventing systemic allergic reactions^{1, 2}; after 5 years of VIT, the clinical protection rate is approximately 98%.³

The immunologic parameters used most frequently to evaluate the response to VIT are the venom-specific IgE and IgG Ab levels and VST. Interpretation of

Abbreviations used

DSC:	Deliberate sting challenge
HB(V):	Honeybee (venom)
VST:	Venom skin test
VIT:	Venom immunotherapy
Ab:	Antibody
WFH:	White-faced hornet
YH:	Yellow hornet
YJ(V):	Yellow jacket (venom)

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published data concerning venom-specific IgE and IgG Ab levels and VST is difficult because of the multiplicity of assay techniques and scoring methods. Both venom-specific IgE Ab levels and VST reactivity slowly decrease during VIT but become completely negative in only a minority of patients.⁴⁻⁶ Preliminary reports exist that VIT may be stopped after 5 years irrespective of the continued presence of venom-specific IgE Ab⁷ or in patients whose IgE Ab levels have declined to insignificant levels.⁸ Moreover, many

TABLE I. Grading of generalized insect-sting reactions*

Grade	Signs and symptoms
I Slight general reaction	Generalized urticaria, itching, malaise, or anxiety
II General reaction	Any of the above plus one or more of the following: Generalized edema Constriction in chest Wheezing Abdominal pain Nausea and vomiting Dizziness
III Severe general reactions	Any of the above plus one or more of the following: Laryngeal edema Dysphagia Hoarseness or thickened speech Confusion or feeling of impending disaster
IV Shock reaction	Any of the above plus one or more of the following: Fall in blood pressure Collapse Incontinence Unconsciousness

*Modified from Mueller et al.¹⁶

insect-allergic patients who do not meet these criteria have received VIT indefinitely, resulting in considerable expenditure of time and money for these patients. Conversely, many insect-allergic patients have stopped VIT, despite continued sensitivity (as judged by VST or venom-specific IgE) and have not sustained a generalized reaction when they were subsequently stung.

The venom-specific IgG Ab level plateaus during maintenance VIT.⁹ Some investigators consider individuals whose IgG Ab levels are low to be at increased risk for reactions to subsequent stings.^{10, 11} In contrast, other investigators have reported patients with low levels of venom-specific IgG Abs who did not react to subsequent stings.¹²⁻¹⁴ Also, the ratio of pre-VIT venom IgG Abs to post-VIT IgG Abs may not be helpful prognostically if the pre-VIT IgG level is already elevated because of a recent sting.¹² When VIT is stopped, IgG levels decline to levels observed in untreated patients,^{6, 13} and yet clinical immunity

TABLE II. Patients' demographic data

No. patients	51
M/F	35/16
Age (yr)	
Range	9-67
Mean	31
Duration of therapy (yr)	
Range	2-10
Mean	5.2
Venom therapy	
YJ	8
HB	4
YJ plus HB	3
Mixed vespid	7
Mixed vespid plus wasp	17
Mixed vespid plus wasp plus honeybee	6
Other	6

persists, making the concept of IgG as the sole protective mediator questionable.

A current recommendation that VIT can be safely stopped after 5 years (despite the continued presence of venom-specific IgE Abs in 89% of patients) is based on a single-center study of 74 patients⁷ whose YJ or mixed vespid maintenance VIT was stopped after 5 to 8 years. Recurrence of sting sensitivity 2 years after VIT was stopped, as judged by DSC, was only 3%. However, further observations in a group of 87 patients who stopped YJ or mixed vespid VIT after 5 years revealed that systemic reactions occurred in 10 patients (11%).¹⁵ The aims of the present collaborative study were to determine (1) whether fewer years of VIT would maintain clinical protection and (2) whether clinical or immunologic parameters exist that could predict either the outcome of DSC or the subsequent clinical course in patients stopping VIT.

MATERIAL AND METHODS

Patients

At the Mayo Clinic, we enrolled 51 self-selected patients from our local practice or from the practices of other allergists in the upper Midwest. All patients had histories of generalized reactions to Hymenoptera stings and positive VST. The pre-VIT reactions were graded by a modification of the classification according to Mueller et al.¹⁶ (Table I). Demographic data are listed in Table II. All patients had received VIT to all the venoms originally producing positive VST; most patients had received mixed vespid and wasp VIT.

Study design

While patients were receiving maintenance VIT, they had DSC from positively identified live insects, and most pa-

TABLE III. Pre-VIT sting data and DSC results

Time	Patients		Grade of reaction			
	Stung	Reactors	I	II	III	IV
Field stings						
Pre-VIT	51	51	10	18	8	15
Deliberate stings						
During VIT	51	0				
After VIT (yr)						
1	51	2	1*			1*
2	16	0				
3	11	0				
4	2	0				
5	2	0				

*Grade IV pre-VIT field-sting reactions.

tients had repeat VST. If the DSCs were tolerated, patients voluntarily stopped VIT, enrolled in the study, and were asked to return annually for repeat VSTs and DSCs. This study design eliminated any patients who were primary VIT failures. Sera were obtained from patients before DSC for measurement of venom-specific (YJ and/or HB) IgE and IgG Ab levels when VIT was stopped and 1 year after VIT was stopped. The study was reviewed and approved by the Mayo Institutional Review Board.

Ninety-nine venom-treated patients had DSC during an 8-year period from 1981 to 1989. However, 28 patients had stopped VIT without providing a serum specimen before our evaluation, and 24 patients were not able to return 1 year after stopping VIT. Therefore, 51 patients were enrolled in the study. The 48 patients not enrolled in the study were similar to the 51 patients of the study with respect to gender, age, duration of VIT, and venoms received (data not presented).

Skin testing

Intradermal VST titrations were performed with commercial venom extracts at 1 µg/ml or less. Sufficient volume was injected to produce an initial wheal 5 mm in diameter. After 15 minutes, the wheal-and-flare diameters were recorded and graded according to the scale of Norman¹⁷; a grade of 1+ or higher was considered positive. A few patients evaluated in the early 1980s did not have VST at the time of DSC.

Sting challenge

Each patient had at least two DSC sessions 1 year apart, one DSC while the patient was still receiving VIT (time 0), and again 1 year later after VIT was stopped (time 1 year). In addition, many of the patients have returned annually for subsequent DSCs. Patients were stung once with each available insect to which they were receiving VIT. For example, patients receiving mixed vespid venom were stung once with a YJ, once with a YH, and once with a WFH. When se-

quential challenges with different insects were done on the same day, they were spaced approximately 60 to 90 minutes apart to allow for delayed reactions. Insects used for DSC were collected from local nests and positively identified by an entomologist. The DSC took place in a clinical research center with readily available resuscitation equipment and emergency medications.

IgE and IgG Ab measurements

Measurements of serum venom-specific IgE and IgG Ab levels were done at the Dermatology, Allergy, and Clinical Immunology Laboratory at The Johns Hopkins University by methods described previously.^{18, 19} Ab levels were measured for YJ and HB venoms only and reported in mass units per milliliter.

Statistical analysis

Nonparametric statistics were used for our data analysis. The signed-rank test was used to analyze differences between Ab levels from time 0 to 1 year. The rank-sum test with log-transformed Ab values was used to analyze Ab differences between groups of patients (patients receiving VIT less than 5 years and patients receiving VIT 5 or more years; patients with negative skin tests at time 0 and patients with positive skin tests at time 0).

RESULTS

Deliberate stings

One year after VIT was stopped, 49 patients who had previously tolerated DSC, while they were receiving VIT, now tolerated another DSC, whereas two patients had generalized reactions (Table III). Of these 49 nonreactors 16, 11, 2, and 2 also returned for DSCs 2, 3, 4, and 5 years, respectively, after VIT was stopped. No additional generalized reactions occurred in any of these patients.

Both reactors had histories of grade IV field-sting

reactions to YJ. One patient had received YJ VIT for 2 years and then sustained a grade I reaction 1 year after stopping VIT. The second patient had received YJ, WFH, and wasp VIT for 4 years and then sustained a grade IV reaction 1 year after stopping VIT. The case histories of these two patients are as follows:

Patient No. 1. This 42-year-old man was first observed at the Mayo Clinic in 1982 for insect-sting allergy. His first sting reaction had occurred 3 months previously, although he had had many previous uneventful stings. This sting reaction began within 20 minutes when he developed erythroderma and pruritus, followed shortly by cutaneous angioedema, generalized urticaria, dyspnea, and hypotension. He responded to treatment with epinephrine and diphenhydramine in the emergency room. Two weeks later, VSTs at another center were strongly positive to vespids but negative to HB. An identical generalized reaction was evoked by the VST and was reversed by treatment with epinephrine and diphenhydramine. When he subsequently started receiving mixed vespid and wasp VIT, he experienced numerous systemic symptoms, even at reduced dosages. VST performed at the time of our evaluation, revealed 3+ to YJ, 2+ to WFH and 1+ to YH venoms at concentrations of 1 ng/ml. Wasp venom was 2+ at a concentration of 10 ng/ml, and HBV was negative. During VST, he developed itchy eyes, nasal blockage, and some dryness and fullness in the mouth that did not require therapy. We considered that YJ was the culprit insect with the reactions to the hornet venoms probably caused by cross-reacting allergens. Because the patient was from out of town and was quite apprehensive about VIT because of his previous experiences, he was hospitalized for approximately 5 days and had a "rush" VIT program. To reduce the number of confounding variables, we opted to treat him only with YJV and to aim for a higher than usual maintenance dose. He subsequently achieved and tolerated a maintenance YJV dose of 200 µg every 5 to 6 weeks. Approximately 2 years later, the patient developed generalized myositis, and the VIT was incriminated by his local physician. A DSC to YJ was tolerated, and VIT was stopped; VSTs were not performed. One year later (after VIT was stopped) VSTs were 1+ to YJ and 2+ to WFH venoms at concentrations of 1 µg/ml, whereas the other venoms were negative. Because of his positive skin tests to multiple vespids before receiving VIT, we elected to perform DSCs with multiple vespids. A deliberate YJ sting produced, within 1 hour, mild itching of the face, lip, and neck. Next, he had a YH sting, and this was followed by a sensation of fullness of the tongue within 15 minutes. Results of his physical examination was unremarkable. After a subsequent wasp sting, he again experienced mild itching of the mouth and neck. These symptoms resolved spontaneously without treatment. WFHs were not available for sting challenge on this day. It was difficult to estimate at this point how much his symptoms were due to only the wasp sting and how much his symptoms reflected a cumulative effect of all three stings. An empiric decision was

made jointly at this time to restart his YJ VIT and add WFH VIT.

Patient No. 2. A 25-year-old woman was first observed at the Mayo Clinic in 1980 for insect-sting allergy. She had been stung several times by unknown insects during childhood with no ill effects. One month before our evaluation, she was stung once on the toe by an insect identified as a YJ. Within 5 to 10 minutes, she experienced angioedema of the palms, visual blurring, lightheadedness, generalized erythroderma, and subsequently passed out. She had epinephrine administered and was subsequently admitted to a local hospital for 5 days. She had recurrent episodes of generalized urticaria and breathing problems during this period and was treated with diphenhydramine and glucocorticoids. At our initial evaluation, VST revealed 2+ reactions to YJ, WFH, and wasp venoms at concentrations of 0.2 µg/ml. She started VIT to YJ, WFH, and wasp. Approximately 4 years later, VIT was stopped after she tolerated DSCs from each of the vespids; VSTs were not performed at this time. She returned 1 year later for repeat DSCs. Her VST then revealed 3+ reactions to YJ, WFH, YH, and wasp venoms at concentrations of 1 µg/ml, whereas HBV remained negative. Approximately 6 minutes after her YJ sting, she complained of dizziness, headache, lightheadedness, and difficulty breathing. Her blood pressure dropped to 70/30; she subsequently exhibited injection of the conjunctival vessels. Epinephrine was administered, and her symptoms gradually subsided during the next 30 to 60 minutes. Because of her skin test reactivity to all vespid venoms, she again started receiving mixed vespid and wasp VIT at her request.

The responses to DSC 1 year after VIT was stopped are illustrated in Fig. 1. The overall generalized reaction rate for our group of 51 patients was 4%. No generalized reactions were observed in the 31 patients who had received VIT for 5 years or more, but in the 20 patients who received VIT less than 5 years, the generalized reaction rate was 10%.

Venom-specific IgE and IgG Abs

Venom-specific IgE and IgG Ab levels, when VIT was stopped, and 1 year later are presented in Table IV. One year after VIT was stopped, the geometric mean IgE and IgG Ab levels to YJV had declined from 2.7 to 2.4 ng/ml (p not significant) and from 8.0 to 3.7 µg/ml ($p = < 0.01$), respectively; for HB venom, from 4.2 to 3.4 ng/ml (p not significant) and from 8.5 to 3.7 µg/ml ($p = < 0.01$), respectively.

When YJ VIT was stopped, the geometric mean venom-specific IgE Ab level was higher (4.2 ng/ml) in patients treated for less than 5 years compared to the geometric mean IgE Ab level (2.1 ng/ml) in patients receiving VIT for 5 years or more ($p = 0.05$).

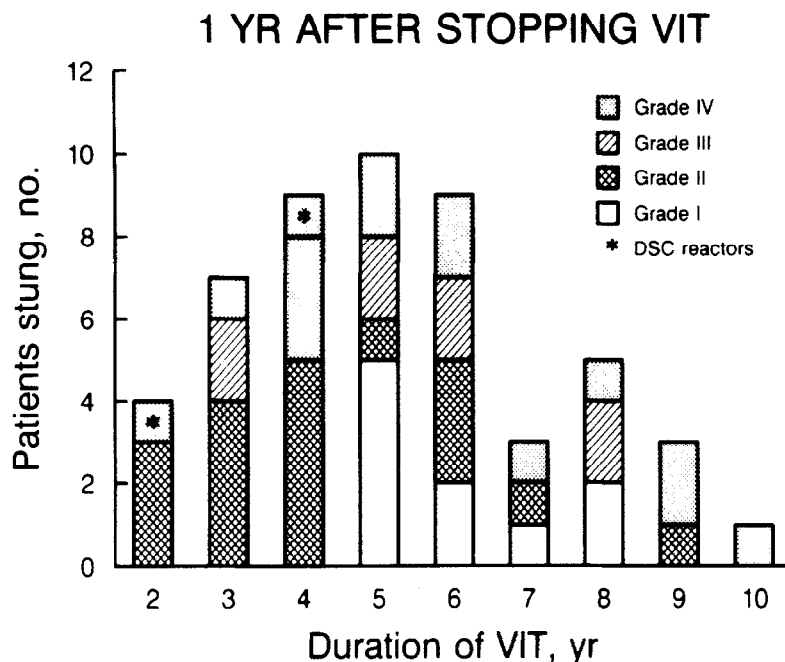


FIG. 1. Responses to DSC 1 year after VIT was stopped in patients treated for 2 to 10 years. The severity of the pre-VIT field-sting reaction is illustrated, and the patients who had a generalized reaction to DSCs are indicated by asterisks.

In the HB VIT-treated patients, the geometric mean IgE Ab level was also higher in the group treated for less than 5 years (8.6 ng/ml) than in the group treated for 5 years or more (2.9 ng/ml), but the difference was not statistically significant, perhaps because of the small number of patients receiving HB VIT. In the year after VIT was stopped, the geometric mean IgE Ab levels in both the YJ- and HB-treated groups did not differ in the groups treated less than 5 years and for 5 years or more. The decrease in IgE levels from time 0 to 1 year in the patients receiving YJ VIT less than 5 years was not statistically significant, but the decrease in the patients receiving YJ VIT for 5 years or more, although they were similar in magnitude, was statistically significant ($p = 0.04$). The decrease in IgE levels from time 0 to 1 year in the patients receiving HB VIT less than 5 years was higher than the decrease in the patients receiving HB VIT 5 years or more ($p = 0.08$).

When YJ VIT was stopped, the geometric mean venom-specific IgG Ab levels did not differ (p not significant) in the groups treated less than 5 years and for 5 years or more. In the year after VIT was stopped, the geometric mean YJ-specific IgG Ab level was lower in the group treated less than 5 years (3.1 $\mu\text{g/ml}$) compared to the geometric mean IgG Ab

level (4.1 $\mu\text{g/ml}$) in patients receiving VIT for 5 years or more ($p = 0.03$). In the HB VIT-treated patients, the geometric mean IgG Ab levels did not differ (p not significant) in the groups treated less than 5 years and for 5 years or more. The decrease in IgG Ab levels from time 0 to 1 year in both the YJ- and HB-treated patients receiving VIT less than 5 years was similar to the decrease in the patients receiving VIT for 5 years or more (p not significant for both).

When patients were grouped on the basis of VST reactivity at time 0, those patients with negative VST had significantly lower geometric mean IgE Ab levels than patients with positive VST. Those patients who received YJ VIT whose YJV skin tests remained positive at time 0 demonstrated a significant decline in geometric mean YJ IgE Ab during the first year after treatment was stopped, whereas geometric mean IgE Ab in the skin test-negative group remained unchanged. In both the YJV- and HBV-treated patients, geometric mean IgG Ab levels were similar in skin-test positive and skin test-negative groups at the time VIT was stopped, and, as expected, decreased to a similar degree during the first year after VIT was stopped in the skin test-positive and skin test-negative groups.

The IgE and IgG Ab levels for the two patients with

TABLE IV. Geometric mean venom-specific IgE and IgG levels (lower and upper boundary) at the time VIT was stopped (0) and 1 year after VIT was stopped (1) in various groups of patients

	IgE (ng/ml)		IgG (μg/ml)	
	0	1	0	1
YJ				
All pts (N = 46)				
Mean	2.7 (2.3, 3.3)	2.4 (2.0, 2.8)	8.0 (7.3, 8.8)	3.7 (3.4, 4.0)*
Range	0.47-231	0.44-141	1.9-30	1.3-15
Pts receiving VIT <5 yr (N = 17)				
Mean	4.2 (3.1, 5.8)	3.9 (2.8, 5.3)	7.4 (6.3, 8.8)	3.1 (2.7, 3.4)*
Range	0.54-231	0.59-141	2.2-26	1.5-12
Pts receiving VIT ≥5 yr (N = 29)				
Mean	2.1 (1.8, 2.6)†	1.8 (1.5, 2.2)‡	8.4 (7.5, 9.4)	4.1 (3.7, 4.6)*§
Range	0.47-28	0.44-15	1.9-30	1.3-15
Pts with pos skin test at time 0 (N = 13)				
Mean	5.7 (3.8, 8.4)	4.3 (2.9, 6.3)†	9.4 (7.6, 11.6)	4.3 (3.5, 5.3)*
Range	1.4-231	0.87-141	2.7-29.8	1.3-14.7
Pts with neg skin test at time 0 (N = 17)				
Mean	1.3 (1.1, 1.5)	1.1 (0.92, 1.4)	6.6 (5.7, 7.6)	3.6 (3.2, 4.1)*
Range	0.47-7.8	0.44-7.0	1.9-15.9	1.5-9.2
Individuals reacting to DSC				
Patient 1	8.2	5.9	13	3.7
Patient 2	2.5	4.9	7.7	1.7
HB				
All pts (N = 15)				
Mean	4.2 (3.1, 5.7)	3.4 (2.5, 4.7)	8.5 (6.8, 10.5)	3.7 (3.1, 4.4)*
Range	0.67-31	0.74-35	2.2-32	1.4-17
Pts receiving VIT <5 yr (N = 5)				
Mean	8.6 (7.2, 10.2)	5.8 (5.1, 6.7)	12.3 (8.8, 17)	3.8 (3.1, 4.6)
Range	5.1-12	3.9-9.0	4.7-28	2.1-6.8
Pts receiving VIT ≥5 yr (N = 10)				
Mean	2.9 (1.9, 4.4)	2.6 (1.7, 4.1)	7.0 (5.4, 9.2)	3.7 (2.9, 4.8)*
Range	0.67-31	0.74-35	2.2-32	1.4-17
Pts with pos skin test at time 0 (N = 6)				
Mean	6.1 (4.7, 8.0)	5.0 (4.0, 6.3)#	7.4 (5.2, 10.5)	3.1 (2.5, 3.8)‡
Range	1.9-12	1.7-9.0	3.0-28	1.5-6.8
Pts with neg skin test at time 0 (N = 5)				
Mean	1.5 (1.0, 2.3)	1.2 (0.86, 1.8)	9.0 (5.4, 15)	4.3 (2.7, 6.7)
Range	0.67-7.1	0.74-5.3	2.2-32	1.4-17.2

pts, Patients; pos, positive; neg, negative.

* $p < 0.01$ for the comparison with time 0.† $p = 0.05$ for the comparison with patients receiving VIT for less than 5 years.‡ $p < 0.05$ for the comparison with time 0.§ $p = 0.03$ for the comparison with patients receiving VIT for less than 5 years.|| $p < 0.01$ for the comparison with patients with negative skin test.¶ $p = 0.05$ for the comparison with patients with negative skin test.# $p = 0.02$ for the comparison with patients with negative skin test.

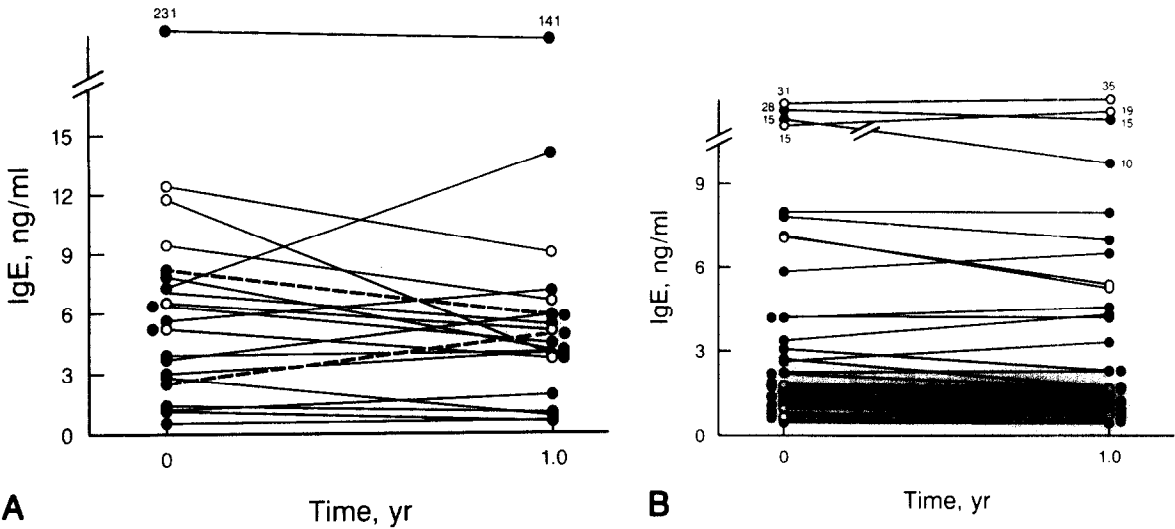


FIG. 2. A, YJ (●) and/or HB (○) IgE Ab levels in 20 individual patients who had received VIT for less than 5 years are listed at the time VIT was stopped and 1 year later; patients without generalized reactions (—); patients with generalized reactions (— — —). **B,** YJ and/or honeybee IgE Ab levels in 31 individual patients who had received VIT for 5 years or more are listed at the time VIT was stopped and 1 year later.

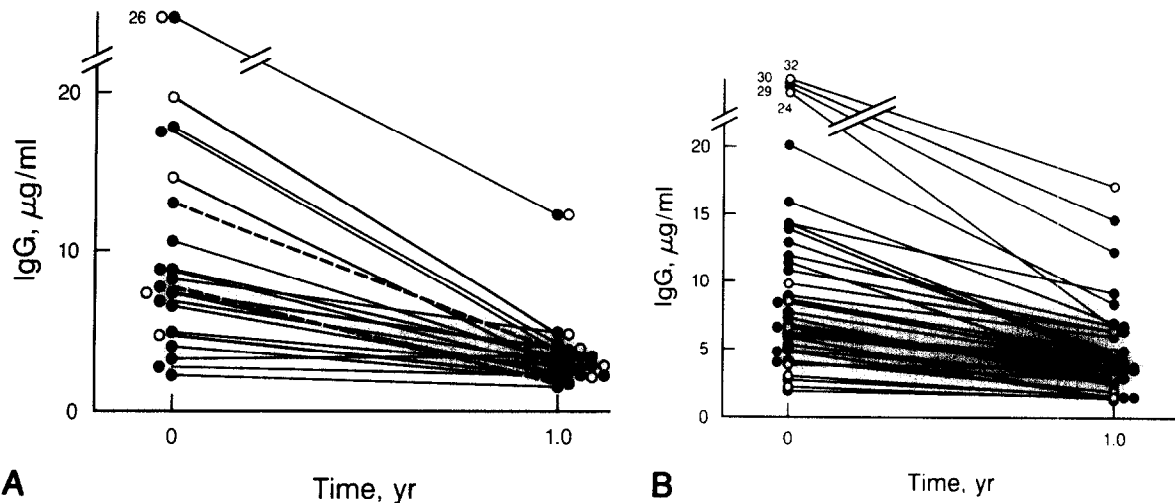


FIG. 3. A, YJ and/or HB IgG Ab levels in 20 individual patients who had received VIT for less than 5 years are listed at the time VIT was stopped and 1 year later. *Symbols* are same as in Fig. 2. **B,** YJ and/or HB IgG Ab levels in 31 individual patients who had received VIT for 5 years or more are listed at the time VIT was stopped and 1 year later.

generalized reactions are also listed in Table IV. With just two such patients it is difficult to assess the significance of their levels; indeed, by inspection, their Ab levels are similar to levels of the other patients. Finally, all individual antivenom IgG and IgE levels are illustrated in Figs. 2 and 3, plotted as a function of time after VIT was stopped.

Skin tests

The VST results in YJ- and HB-sensitive individuals at various times after VIT was stopped are listed in Table V. When VIT was stopped, 17 of 30 YJ-sensitive patients and five of 11 HB-sensitive patients had negative VSTs. Unfortunately, the two patients with generalized reactions were not skin tested when

TABLE V. VST results in YJ- and HB-sensitive patients at various times after VIT is stopped

	Time after VIT is stopped (yr)					
	0 (%)	1 (%)	2 (%)	3 (%)	4 (%)	5 (%)
YJ sensitive						
YJ +	13 (43)*	20 (51)	3 (33)	5 (100)	1 (100)	2 (100)
YJ -	17 (57)	19 (49)	6 (67)	0	0	0
Total	30 (100)	39 (100)	9 (100)	5 (100)	1 (100)	2 (100)
HB sensitive						
HB +	6 (55)	7 (58)	2 (50)	3 (60)		
HB -	5 (45)	5 (42)	2 (50)	2 (40)		
Total	11 (100)	12 (100)	4 (100)	5 (100)		

+, Positive; -, negative.

*Number of patients (percent of total).

VIT was stopped; 1 year later, both patients had positive skin tests to YJ. Overall, there was no change in VST reactivity in 22 of 30 (73%) YJ-sensitive patients and in seven of 10 (70%) HB-sensitive patients 1 year after VIT was stopped. The duration of VIT did not affect VST reactivity after VIT was stopped. VST remained positive in 13 of the 14 patients (93%) who received VIT less than 5 years and in 22 of the 30 patients (73%) who received VIT for 5 years or more.

DISCUSSION

The efficacy of VIT has been well demonstrated in previous studies. Untreated patients with generalized reactions have a 27% to 61% risk of a repeat systemic reaction with future stings.^{1, 19-21} Patients with generalized reactions who have received VIT for 1 or 2 years have approximately a 25% risk of a generalized reaction, and in patients who have received VIT for 5 years or more, the risk drops to approximately 2%.^{3, 6} Our results are similar; we noted generalized reactions in 25% of the four patients who received VIT for only 2 years, in 10% of the 20 patients who received VIT less than 5 years, and an overall incidence in 51 patients of approximately 4%. There were no generalized reactions in the 31 patients who had received VIT for 5 years or more. Our findings support the recommendation that VIT be continued for 5 years, although there are many patients who do well with 3 or 4 years of VIT.

The number of patients who returned for DSCs 2, 3, 4, and 5 years after stopping VIT were 16, 11, 2, and 2, respectively. Many of these patients (14 of 31) had received VIT for less than 5 years, and none of the patients had a systemic reaction with subsequent DSCs. Although the number of patients is small, these results are very encouraging because they suggest that clinical reactivity remains suppressed years after

VIT is stopped and that the recurrence risk may be confined to the first year after VIT is stopped. Moreover, both patients who experienced generalized reactions to DSCs 1 year after stopping VIT had experienced grade IV reactions before beginning VIT. This finding suggests that the duration of VIT recommended should be tailored to the severity of reaction to the pre-VIT field sting, with patients experiencing more severe reactions being treated for at least 5 years. We will need to continue the yearly DSCs in these and additional patients, however, before we can estimate more precisely the risk of recurrence of clinical sensitivity.

The lack of correlation between immunologic reactivity and clinical sensitivity was demonstrated in this study. Venom-specific Ab levels and VST reactivity did not predict which patients could safely stop VIT. At the time VIT was stopped, individual venom-specific IgE and IgG levels were quite variable, and the Ab levels in the two patients with generalized reactions were similar to levels of the DSC-tolerant patients. Venom-specific Ab levels in patients returning for DSCs at 2, 3, 4, and 5 years have not been measured; therefore, we cannot comment on the predictive uses of these assays after VIT has been stopped for more than 1 year. Because data concerning cumulative venom doses received were not routinely collected from referring allergists, we could not correlate cumulative venom doses with either clinical outcomes or immunologic reactivity.

VST results also do not appear to correlate with clinical sensitivity. When VIT was stopped, 13 of 30 YJ-sensitive patients and six of 11 HB-sensitive patients had positive VSTs, and yet none had positive DSCs. At 1 year after VIT was stopped, 20 of 39 YJ-sensitive patients and seven of 12 HB-sensitive patients had positive VSTs with two of the patients also having generalized reactions to DSCs. Not all patients

were skin tested at each visit, and the number of patients studied long term was small; nevertheless, DSC remained negative in many VST-positive patients 2, 3, 4, and even 5 years after VIT was stopped.

The first year after VIT was stopped, a small decline in the mean venom-specific IgE Ab levels was observed (which was statistically insignificant). This progressive decrease of sensitivity has been reported previously.¹³ Mean venom-specific IgE levels were lower in the group of patients receiving VIT for 5 years or more at both time 0 and 1 year after VIT was stopped. However, the decrease in IgE Ab levels in YJ-treated patients from time 0 to 1 year after VIT was stopped was similar in both groups of patients, suggesting that both the duration of VIT and the passage of time alone play a role in the decrease of IgE Ab levels. In the HB-treated patients, there was a larger decrease in IgE Ab levels from time 0 to 1 year after VIT was stopped in the group receiving HB VIT for less than 5 years.

We confirmed previous studies reporting a decrease in the mean venom-specific IgG Ab levels after VIT was stopped. One year after VIT was stopped, the mean IgG Ab level fell to that observed in untreated patients. In our patients, this decrease was statistically significant for both the YJ- and HB-treated patients. Despite this decrease in IgG Ab levels, most patients tolerated DSC, suggesting that "low" levels of IgG Ab do not predispose patients to reactions at this stage of treatment. To evaluate whether duration of VIT influences IgG levels, we compared mean IgG levels between those patients receiving VIT for less than 5 years and those patients receiving VIT for 5 years or more. At time 0, the mean YJ IgG Ab level was higher in the group treated for the longer period, and the mean HB IgG Ab level was higher in the group treated for shorter periods. However, neither of these differences were statistically significant. Venom IgG levels of <3.0 to 5.0 $\mu\text{g/ml}$ early in the maintenance phase of immunotherapy have been reported to be the levels at which individuals are at increased risk for reactions to stings.¹⁰ However, in this study, there were six patients with IgG levels ≤ 3 $\mu\text{g/ml}$ at time 0, and yet none had generalized reactions to DSC.

VST reactivity after VIT was stopped was also variable. In 70% to 75% of patients, the VST reactivity to YJ and HB venom was unchanged. Despite the increase and persistence of VST reactivity, none of these patients experienced a DSC reaction. Unfortunately, the two patients with generalized reactions did not have VST performed when VIT was stopped; thus, changes in their VST reactivity could not be determined.

In summary, $>96\%$ of our group of 51 patients tolerated a DSC 1 year after VIT was stopped. We

suggest that VIT should be continued for 5 years in patients who have experienced pre-VIT field-sting reactions of grade IV severity. An appreciable proportion of patients whose field-sting reactions were of grade I to III severity do well with 3 or 4 years of VIT. However, results from VST or venom-specific IgE or IgG Ab assays did not reliably predict the outcome of DSC or the subsequent clinical course in patients stopping VIT. With only two patients in whom clinical reactivity returned in this series, it is difficult to assess the value of these parameters in predicting protection.

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