

# Long-term protection after stopping venom immunotherapy: Results of re-stings in 200 patients

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**Background:** Venom immunotherapy (VIT) protects most patients allergic to Hymenoptera stings while booster injections are continued. Few data on long-term protection after discontinuation of treatment are available.

**Objective:** We sought to investigate protection from re-stings over a prolonged period after stopping VIT.

**Methods:** Re-sting data were obtained from 200 of 322 patients in whom VIT had been stopped between 1988 and 1992 after a duration of at least 3 years. The 25 (12.5%) patients who again developed systemic allergic reactions were compared with 50 matched patients without re-sting reactions. Clinical data and diagnostic parameters (i.e., skin sensitivity and specific IgE and IgG) were studied.

**Results:** Of the 25 patients who had re-sting reactions, 19 had been treated with bee venom (relapse rate, 15.8%), and six had been treated with *Vespula* venom (relapse rate, 7.5%). About half of the re-sting reactions occurred on the first re-sting after stopping VIT. Most of these reactions were mild, whereas the majority of reactions occurring after repeated re-stings were severe. When re-sting reactions were related to the total re-stings per year, an accumulation of sting reactions was observed in years 3 to 5 after stopping VIT. Patients with re-sting reactions had been receiving VIT for a significantly shorter duration (43.35 months) than those with continued protection (54.65 months) ( $p < 0.01$ ). Of the diagnostic parameters, only a negative intracutaneous skin test at  $10^{-3}$  gm/L predicted long-term protection reliably.

**Conclusion:** Venom immunotherapy of 3 to 5 years duration induces long-term protection in most patients. In rare occasions severe re-sting reactions may, however, occur, especially after repeated re-stings. (J Allergy Clin Immunol 1998; 101:606-12.)

**Key words:** Hymenoptera venom allergy, honeybee venom, *Vespula* venom, venom immunotherapy, long-term protection

Venom immunotherapy (VIT) has been shown to protect most patients with IgE-mediated systemic allergic reactions (SARs) to Hymenoptera stings.<sup>1,2</sup> How long this treatment should be continued is still a matter of debate. Although it was originally proposed to continue VIT for life, this may not be necessary and may meet with problems of compliance and high costs. It was also suggested to stop treatment only in individuals

## Abbreviations used

|       |                                  |
|-------|----------------------------------|
| BV:   | Honeybee venom                   |
| EPC:  | Endpoint concentration           |
| SAR:  | Systemic allergic sting reaction |
| sIgE: | Venom-specific serum IgE         |
| sIgG: | Venom-specific serum IgG         |
| VIT:  | Venom immunotherapy              |
| VV:   | <i>Vespula</i> venom             |

whose diagnostic test results become negative. However, only a small minority of patients will have both negative skin test results and no detectable serum-specific IgE antibodies to venoms even after 3 to 5 years of VIT.<sup>3-5</sup> Patients who stopped VIT of their own accord after only 1 to 2 years seem to be at a relatively high risk of reacting again when re-stung.<sup>6,7</sup> Therefore it is generally agreed that VIT should be continued for at least 3 to 5 years.<sup>2,8</sup>

A number of prospective studies in which patients were rechallenged 1 to 2 years after successful VIT of at least 3 to 5 years duration<sup>9-13</sup> showed that most were still completely protected from re-stings. Patients allergic to vespoid venom did somewhat better than honeybee-sensitive individuals, and children did better than adults. Publications on long-term protection after stopping VIT are still scarce. We report here the results of re-stings in 200 patients up to 7 years after stopping VIT of at least 3 years duration.

## METHODS

### Patients

In the fall of 1995, all 358 patients who had stopped successful VIT between 1988 and 1992 after a duration of at least 3 years were questioned regarding re-stings after discontinuation. Fifty-eight had reported reactions to both honeybee and *Vespula* spp. stings, were sensitive to both venoms, and therefore were treated with honeybee (BV) and *Vespula* venom (VV). Overall, there were 416 VIT treatment courses, 258 with BV and 158 with VV. Data could be obtained concerning 322 treatment courses, 199 with BV and 123 with VV. A total of 200 patients had been re-stung, 120 by honeybees and 80 by *Vespula* spp., resulting in a re-sting rate of 62.1%. Clinical and demographic data on the 200 reexposed patients are presented in Table I.

Atopy was diagnosed before starting VIT on the basis of a history of allergic rhinitis, allergic bronchial asthma, or atopic dermatitis and/or a positive skin prick test response ( $\geq 3$  mm diameter wheal with erythema) to at least one of the following common inhalants: *Dermatophagoides pteronyssinus*, *D. farinae*, grass pollen, birch pollen, artemisia pollen, cat dander, dog

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dander, *Alternaria* spp., or *Cladosporium* spp. (ALK, Horsholm, Denmark).

All patients were instructed regarding differences between honeybees and *Vespula* spp., with the help of color photographs. Of the 200 reexposed patients, 25 reported systemic re-sting reactions, 19 to honeybee and six to *Vespula* spp. stings. All 25 patients with re-sting reactions were called in, tested again, and advised regarding further management of their allergy. For each of the 25 patients with relapse, two control patients who had tolerated the reexposure and were matched for insect, age, sex, and severity of the original reaction were tested as well.

### Venom immunotherapy

All patients were originally treated with Pharmalgen honeybee, *Vespula* spp., or both types of venoms (ALK, Horsholm, Denmark) at a maintenance dose of 100 µg given subcutaneously every 4 weeks during the first year and every 6 weeks during subsequent years. All patients tolerated long-term VIT injections without systemic symptoms, and most had also tolerated either a field sting or a sting challenge by the responsible insect during VIT without any systemic symptoms. The mean treatment duration was 53.4 months (range, 33 to 124 months).

### Skin tests

Intracutaneous skin tests with BV and VV were performed as described previously.<sup>4</sup> The volume of 0.02 ml containing  $10^{-8}$ ,  $10^{-6}$ ,  $10^{-4}$ , and  $10^{-3}$  gm/L venom protein was injected intracutaneously into the volar side of the forearm. The test was considered positive if a wheal of at least 5 mm in diameter with erythema was observed after 15 minutes. The lowest concentration resulting in such a reaction was defined as the endpoint concentration (EPC). Pharmalgen venoms for skin testing were provided by ALK.

### Venom-specific IgE antibodies

In all patients venom-specific IgE (sIgE) antibodies were estimated by Phadezym RAST (Pharmacia & Upjohn Diagnostics, Uppsala, Sweden) before starting and when stopping VIT. In patients with re-sting reactions and re-stung control patients, sIgE antibodies were estimated by IgE immuno-CAP (Pharmacia & Upjohn Diagnostics, Uppsala, Sweden) before and after VIT and after the re-sting. These longitudinal CAP tests were done at the same time with the same allergen matrix. Both tests were performed according to the recommendations of the manufacturer. sIgE antibodies are given in kilounits per liter for IgE Immuno-CAP and in Phadebas RAST units (PRU) for Phadezym RAST.

### Venom-specific IgG antibodies

Specific IgG (sIgG) antibodies to BV and VV were estimated by ELISA as described previously.<sup>4</sup> Results are given in micrograms per milliliter as calculated by comparison with a dilution series of a beekeeper pool or a serum pool from patients allergic to VV receiving VIT, with known content of sIgG antibodies. BV for estimation of specific IgG was obtained from Sigma Chemical Co. (St. Louis, Mo.), and VV (European mix) was obtained from Vespa Laboratories (Spring Mills, Pa.). Longitudinal studies were performed at the same time with the same allergen matrix.

### Statistical analysis

The following unpaired nonparametric data of reexposed patients with and without relapse were compared by the Mann-Whitney U test: age at discontinuation of VIT, duration

**TABLE I.** Demographic and clinical data on 200 patients re-stung after VIT

|                                       | Allergy/VIT to   |                 |
|---------------------------------------|------------------|-----------------|
|                                       | BV               | VV              |
| Number re-stung                       | 120              | 80              |
| Age (MV, range)*                      | 38.9 (11-70)     | 43.4 (12-78)    |
| Sex (M/F)                             | 85/35            | 49/31           |
| Atopy*                                | 24 (20%)         | 16 (20%)        |
| Duration of VIT in months (MV, range) | 54.1 (33-124)    | 52.4 (34-121)   |
| Grade of severity* <sup>14</sup>      |                  |                 |
| I-II                                  | 8 (6.7%)         | 9 (11.3%)       |
| III-IV                                | 112 (93.3%)      | 71 (88.7%)      |
| Skin sensitivity*                     |                  |                 |
| Neg log EPC in gm/L (MV, range)       | 5.83 (3-8)       | 5.15 (3-8)      |
| Venom-specific IgE*                   |                  |                 |
| PRU geom (MV, range)                  | 1.24 (0.35-37.0) | 0.91 (0.35-7.2) |

MV, Arithmetic mean value.

\*Before starting VIT.

of VIT, skin test EPC, sIgE, and sIgG. For comparison of paired nonparametric data, the Wilcoxon signed-rank test was used to compare skin test EPC, specific IgE, and specific IgG before VIT, when stopping VIT, and after reexposure within groups.

Chi square contingency table analysis was used to compare reexposed patients with and without relapse regarding distribution of sex, incidence of atopy, severity of systemic allergic reaction, VIT duration, and insect species. It was also used to compare re-stings with and without systemic allergic reactions regarding their distribution over the 7 years after stopping VIT and to compare the severity of the systemic allergic re-sting reactions with the first versus later re-stings.

### RESULTS

In 200 of 322 VIT courses, re-stings were reported. This high reexposure rate of 62.1% during 3 to 7 years of posttreatment observation reflects the high exposure of our patients, who mostly originate from the countryside.

### Re-sting reactions in 25 patients

Of the 120 re-stung patients allergic to BV, 19 (15.6%) reported systemic allergic re-sting reactions (SARs), and of the 80 patients allergic to VV, six reported SARs (7.5%). In five patients allergic to BV and two patients allergic to VV, symptoms were only subjective, leaving 14 (11.7%) patients allergic to BV and four (5%) patients allergic to VV with objective SARs. The difference in the re-sting reaction rate between individuals allergic to BV and VV does not quite reach statistical significance (chi square = 3.047,  $p = 0.081$ ).

Table II shows details on the re-sting reactions in 19 individuals allergic to BV and six individuals allergic to VV. A number of patients (1, 2, 9, 10, 15, and 19) had more than one re-sting reaction of similar severity; some (9, 14, and 23) also had re-sting reactions of increasing severity. In 14 patients (56%) the reaction occurred after the first re-sting after discontinuation of VIT. In eight

**TABLE II.** Re-sting reactions after stopping VIT in 19 BV-sensitive and 6 VV-sensitive patients

| Patient no.            | M/F | Age* | Severity of reaction |                             | No. of re-stings after VIT | Years after VIT | Duration of VIT (mos) | Restart of VIT |
|------------------------|-----|------|----------------------|-----------------------------|----------------------------|-----------------|-----------------------|----------------|
|                        |     |      | Before VIT           | After VIT                   |                            |                 |                       |                |
| B-V sensitive patients |     |      |                      |                             |                            |                 |                       |                |
| 1                      | M   | 34   | III                  | I U                         | 1-6                        | 1 to 5          | 35                    | Yes            |
| 2                      | F   | 66   | III                  | I dizz                      | 1-16                       | 1 to 5          | 37                    | No             |
| 3                      | M   | 28   | IV                   | I U                         | 1                          | 1               | 40                    | Yes            |
| 4                      | F   | 48   | IV                   | I U                         | 1                          | 1               | 77                    | Yes            |
| 5                      | M   | 18   | IV                   | II U, E                     | 1                          | 2               | 44                    | Yes            |
| 6                      | M   | 49   | IV                   | III P, D, AE                | 1                          | 1               | 36                    | Yes            |
| 7                      | F   | 45   | I                    | I P                         | 1                          | 2               | 35                    | No             |
| 8                      | M   | 15   | III                  | IV U, H, D, UC              | 1                          | 4               | 40                    | Yes            |
| 9                      | M   | 37   | IV                   | I N                         | 1,2                        | 4,4             | 36                    | No             |
| 10                     | M   | 32   | IV                   | III dizz, D                 | 3                          | 5               |                       | Yes            |
|                        |     |      |                      | None                        | 1                          | 1               | 87                    | No             |
| 11                     | F   | 16   | III                  | III P, E, D                 | 2-5                        | 2 to 4          | 60                    | Rec            |
|                        |     |      |                      | None                        | 1                          | 2               | 40                    | No             |
| 12                     | F   | 49   | IV                   | I U                         | 2                          | 3               |                       |                |
|                        |     |      |                      | None                        | 3                          | 4               |                       | No             |
|                        |     |      |                      | None                        | 1                          | 2               | 35                    | No             |
| 13                     | M   | 34   | III                  | I E                         | 2                          | 4               |                       | No             |
|                        |     |      |                      | None                        | 1                          | 4               | 40                    | No             |
| 14                     | M   | 45   | IV                   | III 2 stings, AE, D         | 2-3                        | 5               |                       | Yes            |
|                        |     |      |                      | III 3 stings, U, AE, D      | 1-3                        | 4               | 36                    | Yes            |
| 15                     | F   | 30   | III                  | IV N, H, UC                 | 4                          | 4               | 36                    | Yes            |
|                        |     |      |                      | None                        | 1                          | 2               | 36                    | No             |
|                        |     |      |                      | I P, dizz                   | 2,3                        | 5,5             |                       | No             |
| 16                     | M   | 35   | IV                   | None                        | 1,2,3                      | 1,2,2           | 36                    | No             |
|                        |     |      |                      | I P                         | 4                          | 2               |                       | No             |
| 17                     | F   | 29   | III                  | None                        | 1,2                        | 1,1             | 36                    | No             |
|                        |     |      |                      | III AE, D                   | 3                          | 1               |                       | Rec            |
|                        |     |      |                      | None                        | 4                          | 2               |                       |                |
| 18                     | F   | 60   | III                  | None                        | 1-31                       | 1 to 5          | 38                    | No             |
|                        |     |      |                      | III U, D                    | 32                         | 5               |                       |                |
|                        |     |      |                      | None                        | 33-36                      | 5,6,6           |                       | No             |
| 19                     | M   | 38   | III                  | None                        | 1-119                      | 1 to 2          | 36                    | No             |
|                        |     |      |                      | I N, dizz                   | 120-122                    | 3,3,3           |                       | Yes            |
| V-V sensitive patients |     |      |                      |                             |                            |                 |                       |                |
| 20                     | F   | 45   | IV                   | I P                         | 1                          | 3               | 35                    | No             |
| 21                     | M   | 45   | IV                   | I N                         | 1                          | 3               | 35                    | No             |
| 22                     | F   | 32   | III                  | I E                         | 1                          | 4               | 45                    | No             |
| 23                     | M   | 29   | IV                   | I N, dizz                   | 1                          | 1               | 59                    | No             |
| 24                     | M   | 29   | IV                   | III N, dizz, D              | 2                          | 2               |                       | Yes            |
|                        |     |      |                      | None                        | 1                          | 1               | 36                    | No             |
| 25                     | F   | 58   | IV                   | IV D, H, UC                 | 2                          | 1 + 1 mo        |                       | Yes            |
|                        |     |      |                      | None                        | 1                          | 6               | 34                    | No             |
|                        |     |      |                      | IV D, H, UC after 15 stings | 2-16                       | 6 + 4 mo        |                       | Yes            |

U, Urticaria; P, pruritus; E, erythema; AE, angioedema; D, dyspnea; H, hypotension; UC, unconsciousness; N, nausea; dizz, dizziness; rec, recommended but not accepted by patient.

\*Age at end of VIT.

patients (32%) the first re-sting reaction was observed in the first year after stopping VIT.

SARs, which occurred during the first re-sting after VIT, were mild, corresponding to grade I or II according to Mueller's classification<sup>14, 15</sup> in 11 patients (78.5%) and grade III or IV in three patients. On the other hand, nine of 16 (56%) repeatedly reexposed patients with

relapse developed severe SARs. Statistically, there is a strong trend to an increased severity after repeated re-stings (chi square = 3.77,  $p \approx 0.05$ ). In 16 patients with objective re-sting reactions (64%), restarting of VIT was recommended. In the remaining patients VIT was not resumed because the reactions were either very mild and most often of a subjective nature, with symp-

**TABLE III.** Various clinical parameters in 200 re-stung patients with relapse or continued protection

|                                    | Relapse       | Continued protection | p Value |
|------------------------------------|---------------|----------------------|---------|
| No. of patients                    | 25            | 175                  |         |
| Sex (M/F)                          | 13/12         | 121/54               | NS      |
| Age*                               |               |                      |         |
| ≤16                                | 2 (9%)        | 22                   |         |
| >16                                | 23 (13%)      | 153                  | NS      |
| Atopy                              | 3 (12%)       | 37 (21%)             | NS      |
| Severity of reaction before VIT    |               |                      |         |
| I-II                               | 1 (4%)        | 16 (9.1%)            |         |
| III-IV                             | 24            | 159                  | NS      |
| VIT duration in months (MV, range) | 43.35 (35-87) | 54.65 (33-124)       | <0.01   |
| VIT duration ≤50 months†           | 21            | 97                   |         |
| VIT duration >50 months            | 4             | 78                   | 0.007   |

MV, Arithmetic mean value; NS, not significant.

\*Age at discontinuation of VIT.

†Chi square = 7.382.

toms like pruritus, nausea, and dizziness, or the patients had tolerated a later sting without SAR.

#### Predictive value of clinical parameters

Table III lists a number of clinical parameters of the 25 patients with a relapse of their allergy in comparison with the 175 re-stung but continuously protected patients. No significant difference was found regarding mean age, sex distribution, or incidence of atopic disease between the two groups. Only two of 24 (9%) patients aged 16 years or less at discontinuation of VIT relapsed as compared with 23 of 176 (13%) who were above 16 years of age at this time. The number of children included in this study was obviously too small for statistical analysis. Similarly, the group of patients with only mild systemic reactions before starting VIT was very small. A suspected higher proportion of severe pretreatment reactions in patients with relapse could therefore not be confirmed statistically.

The mean treatment duration of patients with a relapse was significantly lower than that of those with continued protection ( $p < 0.01$ ). Only four of 82 (4.8%) patients who had been treated for more than 50 months had a relapse as compared with 21 of 118 (17.8%) of those with a VIT duration of 50 months or less ( $p = 0.007$ ).

Table IV shows the total re-stings and the SARs over the 7 years after stopping VIT. There is an uneven distribution which is statistically significant (chi square = 23.558,  $p < 0.001$ ), with an accumulation of SARs in years 3 to 5 after stopping VIT.

#### Predictive value of diagnostic parameters

Figs. 1 to 3 show the mean values of skin test EPCs, sIgE levels, and sIgG levels before VIT, at discontinuation of VIT, and after reexposure in 25 patients with relapse and 50 control patients (38 allergic to BV and 12 allergic to VV) who did not react when re-stung after VIT.

Skin test EPC decreased strongly and highly significantly from before to after VIT in the control groups, and somewhat less without reaching statistical significance in the patients with relapses. Thereafter there was a further slow decrease of skin sensitivity, which was, however, not significant. No statistically significant difference between the mean skin sensitivity in patients with relapse as compared with those with continued protection was observed at any of the three observation points. In eight of the 200 (4%) re-stung patients (three allergic to BV and five allergic to VV), skin test results were negative ( $EPC > 10^{-3}$  gm/L) when VIT was stopped. None of them reacted when re-stung.

sIgE antibodies also decreased very significantly during VIT and continued to decrease after stopping treatment. No difference between patients with relapses and those with continued protection was observed at any of the three observation points. In 36 of the 200 (18%) re-stung patients (14 allergic to BV and 22 allergic to VV) no sIgE antibodies ( $<0.35$  PRU) could be detected when VIT was stopped. Of these 36 individuals, four (two allergic to BV and two allergic to VV) still had a SAR when re-stung.

sIgG antibodies increased during VIT and decreased strongly after stopping treatment. Again, there was no significant difference between patients with relapses and control patients regarding sIgG antibody levels at any time point. When VIT was stopped, 24 of 25 patients with relapse had sIgG antibodies above 3  $\mu$ g/ml, and 17 of 25 had IgG antibodies even over 5  $\mu$ g/ml.

Because of the low number of re-sting reactions in the VV group, the changes in diagnostic parameters usually do not reach statistical significance. The trend is, however, the same as in the larger BV group.

#### DISCUSSION

There is general agreement that VIT of 3 or more years duration results in a high protection rate of patients allergic to venom both during<sup>1-3, 16</sup> and in the

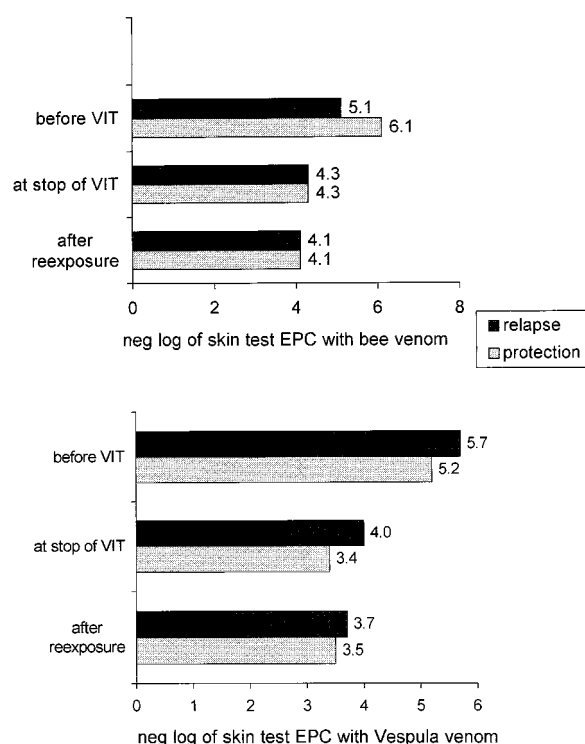


**FIG. 1.** Skin test EPCs (arithmetic mean values) to BV (above) and VV (below) in patients with relapse (BV,  $n = 19$ ; VV,  $n = 6$ ) and continued protection (BV,  $n = 38$ ; VV,  $n = 12$ ). Significant decrease during VIT ( $p < 0.01$ ) is observed in protected patients and patients with relapse on VIT with BV and in protected patients on VIT with VV. No significant difference between patients with relapse and continued protection is found at any time.

first year after stopping this treatment.<sup>9-13</sup> The data on long-term protection after stopping VIT are much more limited and concern mostly patients treated with VV.<sup>17,18</sup> We report here on re-stings in 120 patients allergic to BV and 80 patients allergic to VV during an observation time of up to 7 years after stopping VIT of 3 to 10 years duration. Of the 200 reexposed patients, 25 (12.5%) reported SARs after re-stings. Reisman and Lantner,<sup>17</sup> during an observation time of up to 7 years after stopping VIT, observed SARs in eight of 79 re-stung patients (10.1%), of whom 52 had been treated with VV and 39 with BV. In a more recent paper, Golden et al.<sup>18</sup> report on 74 patients who, after VIT for 5 years duration, were rechallenged at intervals of 1 or 2 years for 5 years. SARs at re-stings were observed in seven (9.5%) of these 74 patients, of whom 62 had been treated with VV. Thus all three studies showed a high protection rate even after up to 7 years after stopping VIT. The somewhat more favorable results in the two American studies may be explained by the fact that they involved mostly VV-sensitive patients, whereas ours dealt with more BV-sensitive patients. The results of VIT with VV are somewhat more favorable than those with BV.<sup>2,16</sup> There are several possible explanations for this apparent difference. A honeybee sting seems to

**TABLE IV.** Distribution of re-stings and systemic reactions 7 years after stopping VIT

| Year | No. of re-stings | No. of systemic reactions* | %    |
|------|------------------|----------------------------|------|
| 1    | 289              | 8                          | 2.7  |
| 2    | 154              | 12                         | 7.8  |
| 3    | 78               | 10                         | 12.8 |
| 4    | 74               | 10                         | 13.5 |
| 5    | 59               | 10                         | 16.9 |
| 6    | 50               | 4                          | 8    |
| 7    | 14               | 1                          | 7    |

\*A number of patients had more than one re-sting reaction. Chi square = 23,558;  $p < 0.001$ .

inject more venom more regularly than a *Vespula* spp. sting.<sup>19</sup> In untreated patients sting challenges with BV result in SARs significantly more frequently than challenges with VV.<sup>20-22</sup> In the United States most VV-sensitive patients are treated with mixed vespoid venoms containing not only VV but also equal amounts of two closely related *Dolichovespula* venoms (*D. arenaria* and *D. maculata*). Thus three times more vespoid venoms are administered than usually given in Europe. Finally, we have included as reactors, unlike other authors, patients with only subjective symptoms (e.g., nausea, dizziness, and pruritus) in this study.

Somewhat more than half of the SARs in our 200 patients occurred after the first re-sting, and most of these were mild. On the other hand, the majority of SARs occurring after repeated re-stings were again severe. An especially intriguing case illustrating this situation is that of patient 24 (see Table II). This 29-year-old farmer had been stung by vespids almost every year, until in 1984 and 1985 he had two SARs to *Vespula* spp. stings, the second being a severe shock reaction. He was treated by VIT with VV from 1987 to 1990 and tolerated repeated *Vespula* spp. stings during the treatment without any systemic symptoms, including a *Vespula* spp. sting challenge in 1990, before stopping VIT. One year later, another *Vespula* spp. sting challenge was well tolerated in our intensive care unit. However, only 4 weeks after this, he was stung by *Vespula* spp. in the fields and developed a severe shock reaction with unconsciousness, which required hospital emergency treatment. As a consequence of this observation, we have given up yearly sting challenges after stopping VIT. The question remains whether sting challenge with VV is really reliable because it has been described,<sup>19</sup> and also observed by ourselves, that *Vespula* spp. may lose part of their venom when caught for the sting challenge. The finding of Golden et al.<sup>23</sup> that five of 30 patients from his original study group<sup>18</sup> had SARs to field re-stings, although four of them had tolerated repeated challenges without any allergic symptoms before, might also be explained by an insufficient venom amount applied in many *Vespula* spp. sting challenges. The observation of Reisman and Lantner<sup>17</sup> that six of their eight patients with SARs after stopping VIT had

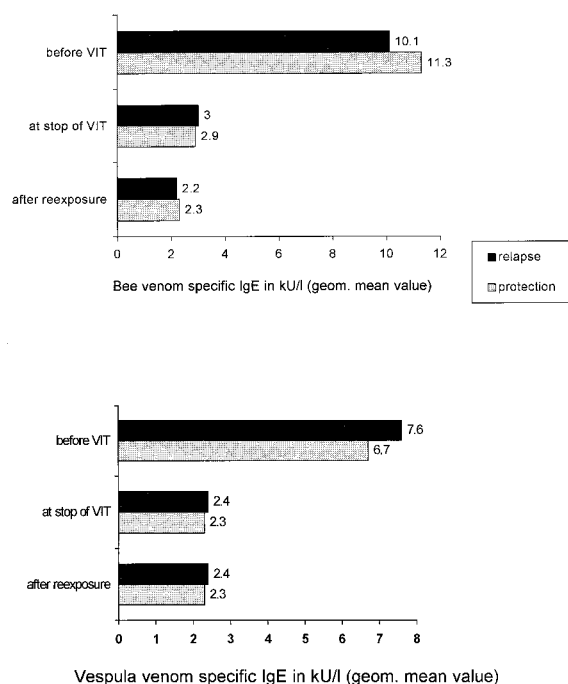


**FIG. 2.** Specific IgE (geometric mean values) to BV (*above*) and VV (*below*) in patients with relapse (BV,  $n = 19$ ; VV,  $n = 6$ ) and continued protection (BV,  $n = 38$ ; VV,  $n = 12$ ). Significant decrease of sIgE during VIT is observed for patients with relapse and continued protection on VIT with BV ( $p < 0.01$ ). There is only an insignificant further decrease after stopping VIT. At no time is there any significant difference between patients with relapse and continued protection.

reactions only after repeated reexposures also points to an increased risk after multiple reexposures after stopping VIT.

Erratic reactions (i.e., systemic sting reactions between well-tolerated stings) as seen in patients 11, 17, and 18 (Table II) have been described previously in studies on the natural history of venom allergy.<sup>5, 16, 22, 24</sup> Variable amounts of venom applied with one sting, as well as a change in the patient's reactivity, may be responsible for such observations.<sup>15</sup> Both patient and doctor are usually ill-motivated to resume VIT after a last well-tolerated sting.

The distribution of SARs in relation to the total number of re-stings in the 200 patients over 7 years was uneven in the sense that there is an accumulation of SARs in years 3 to 5 after stopping VIT. These data have to be judged cautiously, however, because of the wide variation of the observation time after stopping VIT from 3 to 7 years, resulting in high re-sting numbers in the first 3 years after stopping VIT, with decreasing numbers thereafter.

No significant differences were found regarding relapse or continued protection during re-stings in relation to the age at the time of stopping VIT or to the severity of the original SAR before starting VIT. Both the group of children and that of patients with only mild, grade I to

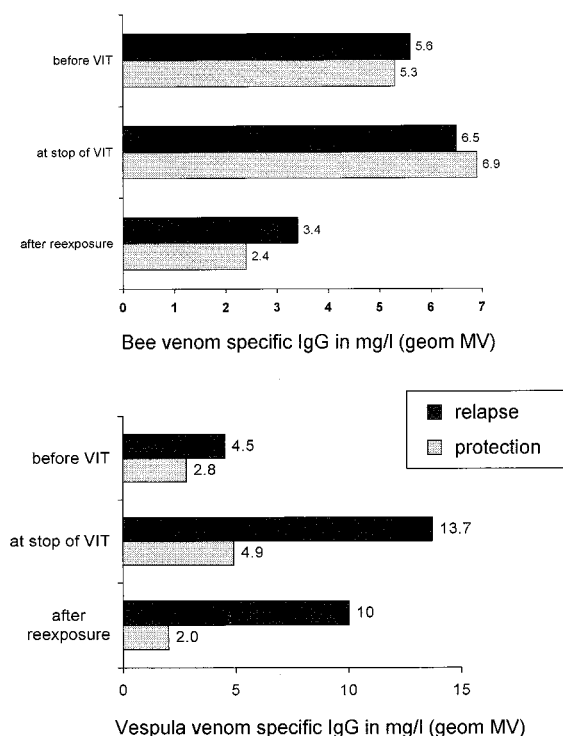


**FIG. 3.** Specific IgG (geometric mean values) to BV (*above*) and VV (*below*) in patients with relapse (BV,  $n = 19$ ; VV,  $n = 6$ ) and continued protection (BV,  $n = 38$ ; VV,  $n = 12$ ). Slight but insignificant increase of sIgG is observed in all groups during VIT and strong decrease after its termination, which reaches statistical significance ( $p < 0.03$ ) in both groups after treatment with BV. At no time is there significant difference between patients with relapse and continued protection.

II systemic reactions before VIT were, however, very small. Therefore a statistical type II error<sup>25</sup> is possible. It seems likely to us that the re-sting risk after VIT is in fact lower in children and in patients with a history of only mild systemic reactions before VIT. The latter has been suggested by several studies on the natural history of venom allergy.<sup>16, 21, 24</sup>

In contrast to our previous publication, in 86 patients allergic to BV rechallenged 1 year after stopping VIT,<sup>11</sup> we found a significantly lower VIT duration in patients with relapse than in those who remained protected. Patients treated for more than 50 months also did significantly better than those treated for between 33 and 50 months. It seems that 3 years and 5 years of VIT do not differ regarding protection in the first year after stopping VIT, but the longer treatment gives superior long-term results. This observation favors a VIT duration of 5 years, at least for adults and for patients with a history of severe reactions.

As previously reported,<sup>9-13, 18</sup> the predictive value of diagnostic parameters obtained at the moment of stopping VIT is very limited. Only a negative intracutaneous skin test result at  $10^{-3}$  gm/L, observed in 8 of the 200 patients (4%), predicted long-term protection reliably.

Neither the absence of sIgE nor high levels of sIgG were of any value in this respect.

In conclusion, our results show that after VIT of 3 to 5 years duration, the vast majority of patients remain protected over a prolonged observation period. Five years of VIT may result in superior long-term protection, and repeated re-stings seem associated with an increased risk of SARs. Resuming VIT is recommended in all patients with objective systemic allergic re-sting reactions.

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