

# Discontinuation of yellow jacket venom immunotherapy: Follow-up of 75 patients by means of deliberate sting challenge

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**Background:** Venom immunotherapy is effective in preventing systemic reactions in patients with a history of an anaphylactic reaction to Hymenoptera stings. It is uncertain how long venom immunotherapy should be continued.

**Objective:** We evaluated whether the duration of venom immunotherapy given to yellow jacket-sensitive patients related to the risk of an anaphylactic reaction to a later sting.

**Methods:** Seventy-five yellow jacket-sensitive patients (29 male and 46 female) received a median number of three in-hospital sting challenges from a live insect in 3 subsequent years after discontinuation of venom immunotherapy. An anaphylactic reaction to one or more of the sting challenges was considered a relapse. We analyzed whether patients with and patients without a relapse differed in terms of gender, age, preimmunotherapy skin test data, preimmunotherapy level of venom-specific IgE, severity of the field-sting reaction that preceded immunotherapy, severity of the reaction to the sting challenge that preceded immunotherapy, adverse reactions to immunotherapy, changes in IgE and IgG<sub>4</sub> levels during immunotherapy, duration of immunotherapy, and presence of venom-specific IgE after cessation of therapy.

**Results:** Venom immunotherapy was given for a median duration of 40 months (range, 7 to 120 months). Relapses were observed in six patients. In two of them, a rather severe anaphylactic reaction was observed after the second sting challenge. No relation was found between duration of venom immunotherapy and relapse risk. The relapse rate was higher among patients with high levels of specific IgE before and after immunotherapy. During therapy, the mean level of specific IgE decreased. This decline persisted in the 3 following years. No relapses of sting reactions were observed among patients without detectable specific IgE.

**Conclusion:** Discontinuation of venom immunotherapy appears safe for patients with pretreatment IgE antibodies if these antibodies can no longer be detected during immunotherapy. For the remaining patients, a treatment period of 3 years may suffice. After discontinuation of immunotherapy, a clinical sting challenge can be considered to estimate the patient's current grade of hypersensitivity. (*J Allergy Clin Immunol* 1997;100:767-70.)

**Key words:** Anaphylaxis, immunotherapy, Hymenoptera, desensitization, yellow jacket, sting challenge

Venom immunotherapy is effective in preventing systemic reactions in patients who have experienced anaphylaxis after a Hymenoptera sting.<sup>1-6</sup> Over the past 2 decades, investigators have sought to refine the treatment schedule. In spite of many publications on the subject, there is still a difference of opinion concerning the optimal therapy regimen (e.g., the way in which the maintenance dose should be reached), the time interval between consecutive booster injections, and the minimal duration of venom immunotherapy.

Two issues that need to be settled are discussed in this report: How long should venom immunotherapy be continued and are there any variables that can predict whether immunotherapy can be safely stopped? Seventy-five patients treated for allergy to yellow jacket venom were subjected to at least one deliberate sting challenge with a live yellow jacket after discontinuation of immunotherapy. Recurrence of anaphylactic symptoms was related to the duration of venom immunotherapy and to clinical and laboratory data.

## METHODS

### Venom immunotherapy

The indication for venom immunotherapy was based on skin test reactivity and concentration of circulating yellow jacket-specific IgE, as well as the severity of the field-sting reaction. Skin tests were performed as described before.<sup>7,8</sup> In short, intracutaneous injections of 0.1 ml solutions with an increasing concentration of purified insect venom (ALK, Copenhagen, Denmark) were given. The lowest concentration of yellow jacket venom at which the induration exceeded 5 mm and the erythema exceeded 10 mm was the skin threshold. Specific IgE levels were measured as described elsewhere.<sup>9</sup> In addition to the skin test and IgE estimation, an in-hospital sting challenge<sup>7,8</sup> was also performed in 29 of the 75 patients.

Detectable insect-specific IgE antibodies, a skin test response positive at 0.1 µg/ml or less, or both were present in 73 patients. The two remaining patients did not have specific antibodies or positive skin test responses; however, they did have a severe anaphylactic reaction (Mueller grade IV<sup>10</sup>) after an in-hospital sting challenge, which was accompanied by high histamine and tryptase levels.<sup>11</sup> Overall, 59 of 75 patients (79%) had experienced a Mueller grade III or IV reaction after a yellow jacket sting.

Venom immunotherapy was started according to the ultrarush method.<sup>12</sup> Yellow jacket venom was injected subcutane-

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**TABLE 1.** All patients who had a systemic reaction after one or more of the challenges after venom immunotherapy

| Patient no. | Age (yr) | Gender | Field-sting reaction | SC reaction before VIT | IgE level before VIT | Duration of VIT (mo) | IgE level after VIT | Post-VIT SC reaction                                                                                                                                                                                                                         |
|-------------|----------|--------|----------------------|------------------------|----------------------|----------------------|---------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1           | 39       | M      | Mueller I            | NP                     | 4+                   | 49                   | 1+                  | Urticaria after first challenge, urticaria and slight edema of the eyelids after second and third challenges                                                                                                                                 |
| 2           | 48       | F      | Mueller IV           | NP                     | 3+                   | 36                   | 3+                  | Generalized itching after first challenge                                                                                                                                                                                                    |
| 3           | 56       | M      | Mueller IV           | MuellerIV              | 4+                   | 60                   | 3+                  | No systemic reaction after first challenge, drop of blood pressure (80/40 mm Hg) and acceleration of pulse rate after second challenge                                                                                                       |
| 4           | 35       | F      | Mueller I            | NP                     | 4+                   | 48                   | 4+                  | No systemic reaction after first challenge, generalized itching and urticaria after second challenge                                                                                                                                         |
| 5           | 58       | F      | Mueller III          | NP                     | 2+                   | 37                   | 2+                  | No systemic reaction after first challenge, no systemic reaction after subsequent field sting, chest pain without electrocardiographic changes, difficulty breathing, generalized urticaria and itching several hours after second challenge |
| 6           | 31       | F      | Mueller III          | NP                     | 4+                   | 30                   | 3+                  | No systemic reaction after first challenge, edema of the eyelids and generalized itching after second challenge                                                                                                                              |

VIT, Venom immunotherapy; SC, sting challenge; NP, not performed.

ously into both upper legs at 30-minute intervals, with the initial dose of venom being one log below the skin threshold. The amount of venom was increased stepwise with log steps up to 1  $\mu$ g. The subsequent doses were 5, 20, 30, 60, and 100  $\mu$ g. Booster injections of 100  $\mu$ g were administered at 7, 21, and 42 days after the onset of hyposensitization and subsequently at 6-week intervals.

### Sting challenge

After voluntary discontinuation of venom immunotherapy, all patients were requested to undergo a sting challenge in 3 subsequent years to evaluate their actual response. A field sting that had occurred after the discontinuation of venom immunotherapy was regarded as a sting challenge. Therefore patients who had experienced one or more field stings received fewer clinical challenges. The severity of the field-sting reaction was estimated by interviewing the patient. Sting challenges were performed in the intensive care unit according to a protocol that has been described previously.<sup>7,8</sup> An anaphylactic reaction was considered a relapse. Before each challenge, blood samples were drawn for determination of yellow jacket-specific IgE and IgG<sub>4</sub> antibodies. IgE levels were measured by means of a RAST assay and expressed semiquantitatively in classes. The RAST classes are related to the percentage of bound radiolabeled anti-IgE (2% to 5% = class 1+, 6% to 10% = class 2+, 11% to 20% = class 3+, 21% to 40% = class 4+, and >40% = class 5+).<sup>9</sup> IgG<sub>4</sub> levels were measured with a similar assay, except that radiolabeled anti-IgG<sub>4</sub>, instead of anti-IgE, was used. These results were expressed in units per milliliter.<sup>13</sup>

### Prospective analysis

All yellow jacket-sensitive patients who had voluntarily discontinued venom immunotherapy and had undergone at least

one postimmunotherapy sting challenge were included in this analysis. The response to postimmunotherapy challenge was compared with the following variables: gender (male vs female), age at the start of venom immunotherapy, preimmunotherapy skin test data (positive at 0.1  $\mu$ g/ml or less vs positive at 1  $\mu$ g/ml or greater), preimmunotherapy level of venom-specific IgE, severity of the field-sting reaction that preceded immunotherapy (Mueller grades I and II vs Mueller grades III and IV),<sup>10</sup> reaction to the sting challenge that preceded immunotherapy, adverse reactions to ultrarush therapy and booster injections, changes in IgE level during immunotherapy, changes in IgG<sub>4</sub> level during immunotherapy, duration of immunotherapy, and presence of venom-specific IgE after cessation of immunotherapy.

### Statistical analysis

The occurrence of missing skin test and IgE/IgG<sub>4</sub> data was random. To analyze the relationship between qualitative variables and relapse risk, we performed the Yates-corrected chi-square test. To analyze the relation between continuous variables and relapse risk, we used the Mann-Whitney U test.

### RESULTS

At the time of this study, 80 patients had discontinued the regular booster injections of venom immunotherapy. Five of them had neither had sting challenge nor experienced a field sting. The analysis therefore included 75 patients. Twenty-nine were men and 46 women. Their median age at the start of venom immunotherapy was 43 years (range, 12 to 75 years). Venom immunotherapy was given for a median duration of 40 months (range, 7 to 120 months). The indication for therapy had been

based on the severity of the reaction to a sting challenge in 29 patients and on the severity of the field-sting reaction in the remaining 46 patients. After discontinuation of venom immunotherapy, 11 patients were challenged once, 15 patients were challenged in 2 successive years, and 49 patients were challenged in 3 successive years. In the meantime, 13 patients experienced a total of 15 field stings that had caused only local reactions.

One hundred eighty-eight sting challenges were performed and eight systemic reactions were observed in six patients. None of these patients had experienced adverse reactions during venom immunotherapy. The overall relapse rate was 8% (6 of 75 patients). The characteristics of the patients with a systemic reaction are described in Table I. In patients 3 and 5, a rather severe anaphylactic reaction was observed after the second sting challenge.

As illustrated in Table II, the relapse rate appeared higher among patients with a high preimmunotherapy level of specific IgE ( $\geq 3+$ ) than among patients with a lower level (chi-square = 10.24; 1 df;  $p < 0.01$ ). For the entire group of patients, the mean level of IgE decreased from  $2.7 \pm 1.35$  (SD) before venom immunotherapy to  $1.8 \pm 1.16$  after cessation of therapy. From the first to the third sting challenge, a further decline to  $1.6 \pm 1.18$  was observed. Of the five patients with undetectable preimmunotherapy levels of IgE, three showed positive RAST results during immunotherapy. In the other two patients, IgE remained undetectable. None of these five patients had a relapse.

Patients with a decrease in specific IgE levels during immunotherapy showed a lower relapse rate than those without, but this difference was not significant (chi-square = 3.76; 1 df;  $p < 0.10$ ). The relapse rate was higher for patients with a high postimmunotherapy level of specific IgE ( $\geq 3+$ ) than for patients with a lower level (chi-square = 9.57; 1 df;  $p < 0.01$ ). At the time of the first sting challenge, no venom-specific IgE could be detected in 21% of patients. At the time of the third challenge, this percentage had increased to 33%. No relapses of sting reactions were observed among patients without detectable specific IgE after cessation of immunotherapy.

Gender, age, severity of the field-sting reaction that preceded venom immunotherapy (Mueller grades I and II vs Mueller grades III and IV), skin test reactivity before immunotherapy (positive at 0.1  $\mu$ /ml or less vs positive at 1  $\mu$ g/ml or greater), change in IgG<sub>4</sub> level during immunotherapy, and duration of therapy appeared not to be related to the relapse risk.

## DISCUSSION

Our study comprises 75 patients who received venom immunotherapy because of yellow jacket sting-induced anaphylaxis. Because they were all sting-challenged after discontinuation of immunotherapy, the efficacy of the treatment could be reliably estimated. Ninety-two percent of the patients appeared to have lasting protection. The relatively high reaction rate of 8% may be partly

**TABLE II.** Relapse rate after cessation of venom immunotherapy according to different variables

|                                                  | No relapse    | Relapse      |
|--------------------------------------------------|---------------|--------------|
| Gender                                           |               |              |
| M                                                | <i>n</i> = 27 | <i>n</i> = 2 |
| F                                                | <i>n</i> = 42 | <i>n</i> = 4 |
| Median age (yr)                                  | 43            | 42           |
| Grade of field-sting reaction that indicated VIT |               |              |
| Mueller I or II                                  | <i>n</i> = 14 | <i>n</i> = 2 |
| Mueller III or IV                                | <i>n</i> = 55 | <i>n</i> = 4 |
| Venom-specific IgE level before VIT              |               |              |
| Undetectable                                     | <i>n</i> = 5  | <i>n</i> = 0 |
| 1+ - 2+                                          | <i>n</i> = 22 | <i>n</i> = 1 |
| 3+ - more                                        | <i>n</i> = 32 | <i>n</i> = 5 |
| Unknown                                          | <i>n</i> = 10 | <i>n</i> = 0 |
| Median duration of VIT (mo)                      | 40            | 41           |
| Change in venom-specific IgE level during VIT    |               |              |
| Decreased                                        | <i>n</i> = 36 | <i>n</i> = 3 |
| Not decreased                                    | <i>n</i> = 17 | <i>n</i> = 3 |
| Unknown                                          | <i>n</i> = 16 | <i>n</i> = 0 |
| IgE level after cessation of VIT                 |               |              |
| Undetectable                                     | <i>n</i> = 13 | <i>n</i> = 0 |
| 1+ - 2+                                          | <i>n</i> = 36 | <i>n</i> = 3 |
| 3+ - more                                        | <i>n</i> = 15 | <i>n</i> = 3 |
| Unknown                                          | <i>n</i> = 5  | <i>n</i> = 0 |

VIT, venom immunotherapy.

due to our strict selection criteria. One third of patients had received venom immunotherapy because of a serious (i.e., Mueller grade III or IV) anaphylactic reaction after in-hospital sting challenge, and generally speaking, the majority of patients (79%) had undergone immunotherapy because of a serious sting reaction, either in the field or in the hospital. In a comparable study by Golden et al.,<sup>14</sup> the relapse rate was 10%.

The purpose of our study was to evaluate whether there are certain criteria that predict a relapse after discontinuation of venom immunotherapy. The studies performed so far, including ours, have some weaknesses in common. First, the overall number of patients studied was small, and only a few patients experienced a relapse. Second, several studies have revealed that in many patients, insect sting anaphylaxis is a self-limiting disease.<sup>15-17</sup> Third, the choice of whether or not to stop immunotherapy was based on different reasons. Therefore conclusions should be drawn with caution.

Of the 75 patients we studied, two had a potentially life-threatening reaction after discontinuation of venom immunotherapy. We therefore remain curious about whether such a relapse can be predicted by some parameter. Skin-test reactivity and insect-specific IgE antibody concentration would be the first variables to consider. However, both have shown a poor correlation with the grade of clinical hypersensitivity.<sup>18-20</sup> Our data clearly show that venom immunotherapy can be safely discontinued in patients with detectable preimmunotherapy IgE antibodies

if these antibodies disappear during treatment. This finding, however, warrants confirmation by identical studies. On the other hand, 51 of the 57 patients (89%) with detectable specific IgE also appeared to be protected. It therefore appears unnecessary to await the absence of IgE antibodies for all patients. We did not study the relation between skin-test reactivity and relapse rate, nor have other studies reported such a relationship.

None of the other variables we tested, including the duration of immunotherapy, appeared to be related to the risk of a relapse. In the literature we found two other possible prognostic factors. Keating et al.<sup>18</sup> and Reisman<sup>21</sup> concluded from their results that patients with a serious field-sting reaction before venom immunotherapy were more at risk of developing a postimmunotherapy relapse. The fact that we did not find the same result could be explained by the high percentage of patients who had received immunotherapy because of a serious anaphylactic reaction. In a study of 86 patients who had received honeybee venom immunotherapy, Müller et al.<sup>22</sup> concluded that the occurrence of systemic reactions during immunotherapy was a negative prognostic indicator of long-lasting protection. Our results do not support this finding because none of the patients who had a relapse experienced adverse reactions during treatment.

In conclusion, the decision as to when to discontinue venom immunotherapy cannot be facilitated by a single parameter. For patients without insect-specific IgE, discontinuation of immunotherapy appears safe, although this finding warrants confirmation by other studies. For the other patients, the treatment should be continued for a period that is known to be related to an acceptable relapse risk. Most authors consider a duration of 3 to 5 years long enough.<sup>14, 18, 23</sup> For the individual patient, a sting challenge can serve to estimate the current grade of hypersensitivity.<sup>24</sup> The usefulness of this test has been confirmed by others.<sup>14, 18, 22, 25</sup> Because the efficacy of venom immunotherapy generally exceeds 95%, some authors doubt whether all patients should be sting-challenged after discontinuation of therapy. Because two of our patients had a potentially life-threatening relapse, we consider a sting challenge justified for patients who have received venom immunotherapy. It is uncertain how many subsequent challenges should be performed. In our study the highest incidence of systemic reactions ( $n = 4$ ) was found at the second sting challenge, but no rise in IgE was observed. The possibility of resensitization can neither be confirmed nor ruled out. However, the finding by Golden et al.<sup>14</sup> that sting challenges did not influence the changes in IgE over time makes resensitization less probable.

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